"I would have everie man write what he knowes and no more."—MONTAIGNE

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EDITORIAL

THE late Professor J. S. Haldane defined the death of the body as "The mysterious dissolution of the association together of the infinitely complex group of normals which constitute the life—the φυσις—of an organism". And so on the contrary the life of an organism, as for example the *British Journal of Anaesthesia*, depends on the association together of the great variety of those interested in the journal. First of all our subscribers, our readers (not always the same people unfortunately), our contributors, our critics, our Board of Management and our publishers. Since the Journal has become a monthly issue there is obviously more scope for correspondents and critics. When the Journal appeared three months hence a critic might very well have time to repent of the hasty words that he had written on the spur of the moment and apt to believe when he saw them in print, after so long an interval, that it was impossible to suppose that he could ever have written them. "Beware when all men speak well of you" is a maxim of which hitherto we have had no occasion to take account, but "Blame is safer than praise" would seem to indicate that we are on right lines. When we receive complaints, as we not infrequently do, our critics must not think that we take no notice of them if their letters are not published. The language in which they are couched, as sometimes happens in the case of foreign correspondents, is interesting and amusing but bears only a slight resemblance to English; at other times, when the source is native, there is a somewhat nearer approach to the mother tongue, but in mercy for the reputation of the critic it has to be withheld. Our contributors are all important and the the Members of the Board, many of whom come continually into the last category, offer us advice and suggestions of the greatest value.

SIR Benjamin Ward Richardson, M.D., F.R.S., was a versatile genius who can be regarded as a patriarch of several branches of medicine. Born in 1828 in a village in Rutland, he was a student at Glasgow at the time of the introduction of anaesthesia and witnessed one of the earliest operations under ether in that city. He died in 1896, and he is reported as saying in the last year of his life, "For a good half-century, it [anaesthesia] has never gone out of my mind or out of my work."

Although he built up a considerable anaesthetic practice in London, his interests were so wide that he could not let himself be bound to any one specialty. Physiology, pathology, medicine, and public health, all owe a debt to this indefatigable man, who was wont to deny that he knew the meaning of the word "tired". His interest in both epedimiology and anaesthesia led to his friendship with John

Snow, who died when his book *On Chloroform and other Anaesthetics* was barely finished. Richardson edited his friend's *magnum opus*, prefaced a biography of Snow, and gave it to the world.

Richardson's activities in the field of anaesthesia were manifold. He was an adviser to the so-called "1864 Committee" appointed by the Royal Medical and Chirurgical Society to enquire into deaths from chloroform. He introduced no less than fourteen new anaesthetic agents, most important of which were the bichloride of methylene, with which Spencer Wells was so pleased that he used it for twenty years, and "methylene ether", which was popular with Lawson Tait. He devised several new pieces of apparatus, especially the ether spray for local refrigeration. He made other researches into local anaesthesia, and designed a "painless knife" with a rotary blade. He was an outspoken opponent to the use of nitrous oxide on account of the asphyxia which accompanied its use, and he made valuable studies of the action of chloral hydrate.

His most important contributions to therapeutics were the introduction of amyl nitrate and of hydrogen peroxide.

A teetotaler, something of a bigot, he was nevertheless an example of the best type of Victorian Englishman, eminent by reason of his personal qualities, not by the mere accident of birth.

His work and writing occupied much time, but he also studied the history of medicine: his collection of biographical essays, first published in the quarterly journal *Asclepiad*, to which for twelve years he was the sole contributor, was published posthumously under the title *Disciples of Æsculapius* and is a valuable addition to the literature of medical history.

The author of *Ecclesiasticus* says that "The wisdom of the scribe cometh by opportunity and leisure; and he that hath little business shall become wise". Richardson was the living antithesis of this idea; in spite of "holding the plough", he nevertheless "sought out the wisdom of the ancients, and kept the discourse of men of renown."

He received the accolade of knighthood in 1893; the *British Journal of Anaesthesia* is proud to adorn the cover of this issue with the portrait of one of the Fathers of Anaesthesia, whom Queen Victoria delighted to honour.

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THE ANTISIALOGOGUE EFFECT OF ANTRENYL (OXYPHENONIUM BROMIDE)

BY

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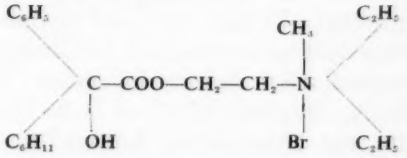
THE depression of salivary secretion by an atropine-like drug before the administration of an anaesthetic is regarded as so important that the inadvertent omission of this drug is either corrected by intravenous administration or is considered sufficient reason for delaying the operation. It is therefore a matter of constant interest to anaesthetists and pharmacologists alike to be on the look-out not only for similar drugs which might have some advantage over atropine, as for example a more pronounced antisalivary effect with less cardiac and intestinal effect, but also for easily and cheaply produced synthetic substitutes for the natural alkaloid itself.

Within the last few years a number of anticholinergic drugs have been synthesized, and investigated as substitutes for atropine, but largely with the treatment of peptic ulcer in mind. One of these is Antrenyl or oxyphenonium bromide. This substance is a benzilic ester of the general formula (Ing, 1946):

$$(C_6H_5)_2\ C(OH).COO(CH_2)_nNRR'R''\}X$$

Where R R′ R″ are alkyl groups, X is a haline anion and n = 2 or 3.

In the case of Antrenyl this formula becomes:



Antrenyl is a crystalline substance with a melting point of about 190°C readily soluble in water. Its pharmacological action is similar to that of anticholinergic substances in general on organs innervated by parasympathetic nerves, and therefore resembles that of atropine. In experiments with animal visceral smooth muscle Antrenyl is twice as potent as atropine in releasing spasm induced by acetylcholine (Bein *et al.*, 1952). Antrenyl and atropine are equipotent in inhibiting the salivation produced by faradic stimulation of the *chorda tympani* in cats, though Antrenyl is a little less so in antagonizing pilocarpine (Plummer *et al.*, 1953).

Clinically, Antrenyl has so far been used for the treatment of peptic ulcer. Here its effectiveness lies in its ability to suppress gastric motility and secretion. Some observers doubt that it has any superiority over atropine (Rowen *et al.*, 1953) while others claim that it has advantages over atropine in that, for

example, effective doses for this purpose produce little or no dryness of the mouth (Plummer *et al.*, 1953). In general the side effects which have been observed when treating peptic ulceration with Antrenyl are xerostomia, blurring of vision, difficulties with micturition, constipation, and occasional dizziness or malaise (Mattman *et al.*, 1953; Rowen *et al.*, 1953).

We have been interested as anaesthetists in the antisialogogue action of Antrenyl. In fact, Antrenyl has already been used as a substitute for atropine as premedication before inhalation anaesthesia. Stephen (1954), of Duke University, has administered Antrenyl in doses of 0.5–1 mg subcutaneously to over 6,000 patients with complete satisfaction to himself as anaesthetist. In these doses, Antrenyl was an effective substitute for atropine, with, in the opinion of Stephen, an antisialogogue potency and duration in excess of that of the usual 0.65 mg (1/100 grain) dose of atropine. Electrocardiographic studies showed no effects different from that of atropine. Pulse and blood pressure observations also showed no changes that were different from those seen with atropine. That an experienced anaesthetist has taken to using Antrenyl as a routine substitute for atropine is, at any rate, strong evidence that serious untoward side effects, or contra-indications to its use for this purpose must be rare. Stephen's estimation of the intensity of the antisalivary action of Antrenyl was, however, made by clinical observation alone.

A method has already been described (Mushin *et al.*, 1953) for measuring with some degree of accuracy the antisialogogue effect of atropine or similar substances. In brief, the method consists of stimulating salivation with a known quantity of fresh lemon juice and measuring the quantity of saliva secreted during a fixed time by rinsing the mouth with a known volume of water. The test is repeated at twenty-minute intervals. The volume of saliva secreted can be easily measured to within a tenth of a millilitre. The data obtained by this method have proved to have a high degree of constancy, reliability and accuracy. This method was used to obtain the results presented in this paper.

In making the comparison, the same dose of Antrenyl was administered subcutaneously as is commonly given clinically in the case of atropine, namely 0.65 mg (1/100 grain). Seven healthy adult volunteers formed the basis of these experiments. The results are shown in figure 1. In each instance several readings were taken before the Antrenyl was injected, and the average of these pre-injection values was taken to be 100 per cent salivary activity. The results obtained after injection were converted into percentages of this normal value. For purposes of comparison figure 2 is reproduced from the paper by Mushin *et al.* (1953). This graph was compiled from a large number of experiments on different subjects and represents a statistically reliable picture. It can be seen from figure 1 that the peak action of Antrenyl is reached in about one hour, after which time the effect falls off, the salivation returning to normal in about four to five hours. At the peak effect there is only 20–40 per cent of normal salivary activity. In general, the effect-time curve shows little difference from that obtained with atropine salts, having regard to the fact

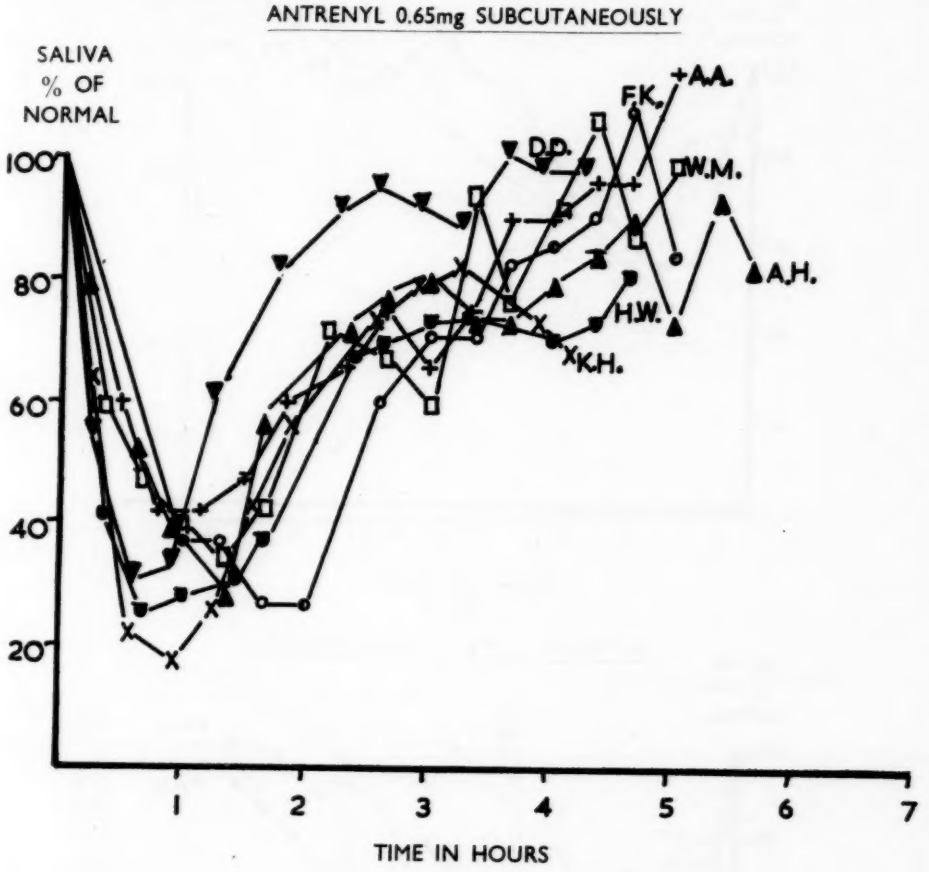


FIG. 1

that with Antrenyl the volunteers had a wide range of body weights, though there appears to be a somewhat greater peak depression of salivary activity and a slightly later return to normal. In the further experiments shown in figures 3 and 4, doses of 1 mg and 2 mg were given to certain of the volunteers. The expected increase in depression of salivary secretion and corresponding increase in the time taken to return to normal are shown. For example, in the case of figure 4, 2 mg given to A.A., weighing 84 kg, produced almost complete inhibition of salivary secretion. Table I gives the weights of the volunteers. The various doses were converted into a mg/kg body weight ratio and plotted on a logarithmic scale in figure 5 against peak effect. A normal sigmoid curve has been fitted to the points. The small degree of

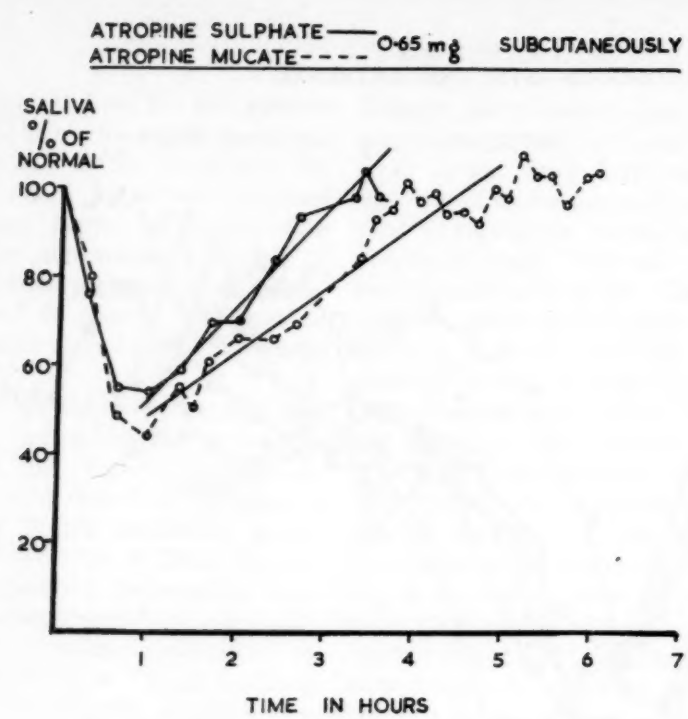

ATROPINE SULPHATE —— 0·65 mg SUBCUTANEOUSLY
ATROPINE MUCATE - - - -
SALIVA % OF NORMAL
100
80
60
40
20
1
2
3
4
5
6
7
TIME IN HOURS

FIG. 2

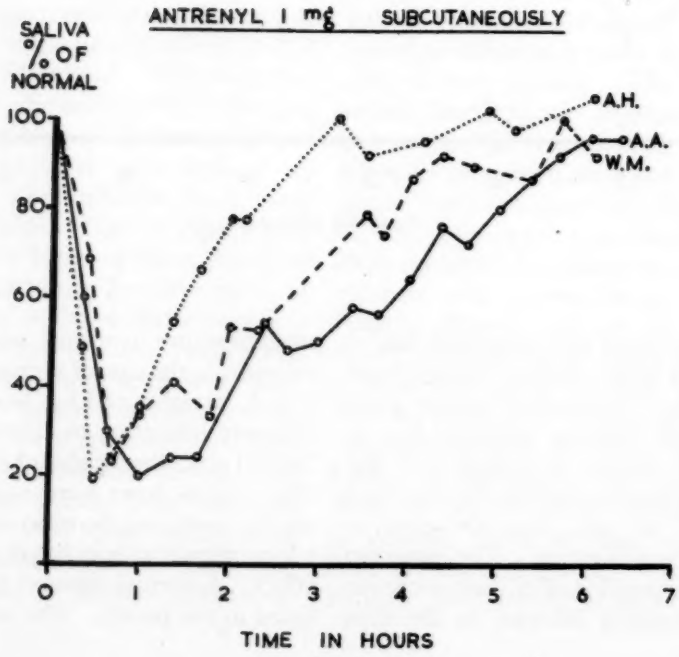

ANTRENYL 1 mg SUBCUTANEOUSLY
SALIVA % OF NORMAL
100
80
60
40
20
A.H.
A.A.
W.M.
0
1
2
3
4
5
6
7
TIME IN HOURS

FIG. 3

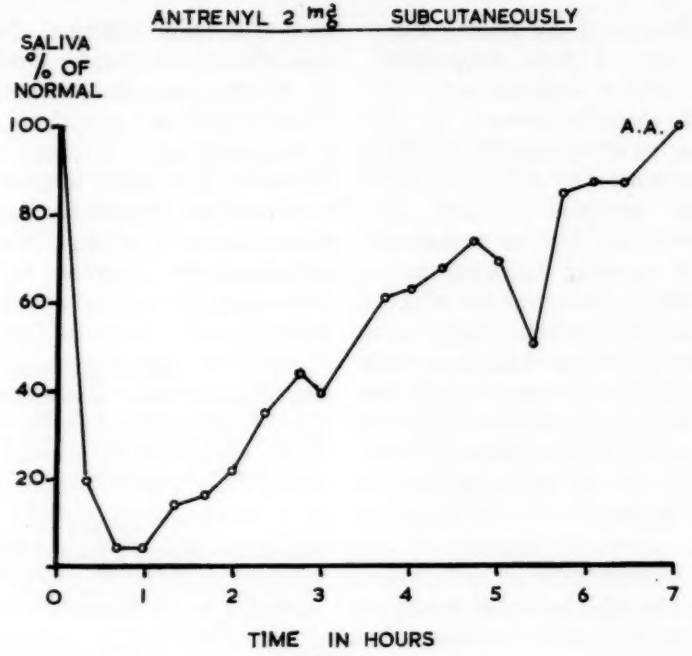


FIG. 4

TABLE I

Subject	Weight in kg
H.W.	58
K.H.	60
F.K.	65
W.M.	69
D.D.	73
A.H.	74
A.A.	84

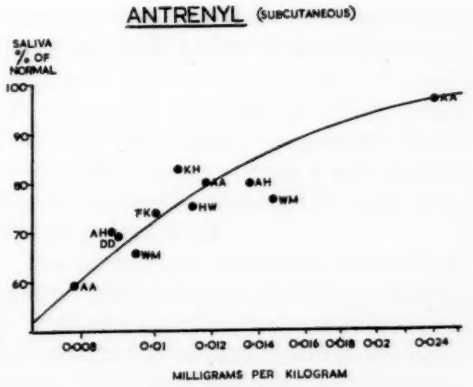


FIG. 5

scatter of the points from this curve supports the reliability of the observations, and suggests that the dose-effect curve is in fact a normal sigmoid, as is common for many drugs.

To test the claim that Antrenyl given orally, as in the treatment of peptic ulcer, causes little dryness of the mouth, we administered doses of up to 10 mg, i.e. nearly sixteen times the subcutaneous dose, to several of the volunteers. The effect on salivary secretion was so small that it could not be measured with the test referred to.

There were no subjective side effects

(other than dryness of the mouth) due to Antrenyl in any of these experiments. None of the subjects reported any interference with accommodation or any cardiovascular or intestinal effects. Pulse rate counts were not very different to those obtained with atropine. In any case, experience with this type of experiment in the case of atropine indicated that so far as the pulse is concerned the effect of environmental factors was likely to be large compared with that of the drug itself. One striking difference was noted by two volunteers who had taken part in the the original atropine experiments. Drowsiness was noticed with atropine, but not noticed with Antrenyl.

SUMMARY

The antisialogogue action of Antrenyl, a synthetic anticholinergic substance, has been measured by the method of Mushin *et al.* (1953). Antrenyl was found to be slightly more potent and to have a slightly longer duration of effect than the same dose of atropine sulphate. No subjective side effects were noted. Oral doses of up to sixteen times the subcutaneous dose failed to give any recordable interference with salivation. Clinical use of this substance in a large number of patients confirms that Antrenyl in doses similar to that of atropine sulphate is a satisfactory substitute for atropine as a means of depressing salivary secretion before anaesthesia.

ACKNOWLEDGMENTS

We record our thanks to Messrs. Ciba Laboratories for supplies of Antrenyl, to K. Hillard, L.I.B.S.T., for technical assistance and for drawing the graphs, to W. W. Mapleson, Ph.D., for fitting the dose-effect curve, and to our volunteers.

REFERENCES

Bein, H. J., Gross, F., Schuler, W., and Tripod, J. (1952). *Schweiz. med. Wschr.*, **82**, 1143.
Ing, H. R. (1946). *Brit. med. Bull.*, **4**, 91.
Mattman, P. E., and Strutner, L. (1953). *Amer. J. dig. Dis.*, **20**, 126.
Mushin, W. W., Galloon, S., and Lewis-Faning, E. (1953). *Brit. med. J.*, **2**, 652.
Plummer, A. J., Bassett, W. E., Rutledge, R., and Yonkman, F. F. (1953). *J. Pharmacol.*, **108**, 292.
Rowen, R. R., Bachrach, W. H., Halsted, J. A., and Shapiro, H. (1953). *Gastroenterology*, **24**, 86.
Stephen, R. (1955). Personal communication.

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STAGES OF "CURARIZATION"

BY

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CURARE is the principal member of a group of drugs which may be used to produce neuromuscular paralysis. Stages in the onset of curarization have been described by Claude Bernard (1856), Vulpian (1870), and Bremer and Titeca (1927). The purpose of this paper is to describe stages of "curarization in relation to d-tubocurarine chloride, gallamine triethiodide, and decamethonium iodide.

Claude Bernard (1856) described a state of curarization in which muscle no longer responded to indirect stimulation through its nerve, but still responded to direct stimulation.

Vulpian (1870) described a state of curarization in which voluntary and reflex movements were absent in the experimental animal, but electrical stimulation of a nerve produced contraction of the supplied muscle.

Bremer and Titeca (1927) carried out experiments both on intact and on decerebrate mammals. The effect of injecting small doses of curare is described as follows: "La flaccidité de l'animal ainsi lègèrement curarisé contraste avec la vivacité et la vigeur de ses réflexes et avec la regularité de sa respiration."

It is clear that these descriptions apply to different stages in the action of the drugs. Which stage is present in a patient at any particular time will depend on the dose given and on the time which has elapsed since it was given. The stages are distinguished by reference to alteration in reflexes and alteration in the response to stimulation of peripheral nerves. This suggested that observation of the effect of specific relaxant drugs on the tendon-jerks and on the response to stimulation of peripheral nerves might provide in man a basis for distinguishing stages of "curarization".

TECHNIQUE

The patients tested were usually premedicated with papaveratum 1/3 grain (20 mg.) and scopolamine 1/150 grain (0.45 mg). For elderly, abnormally small, or physically poor patients, a less depressant combination of morphine and atropine was substituted.

The anaesthetic technique used was as follows: pethidine hydrochloride, usually 50 mg, was given intravenously at least five minutes before the induction of anaesthesia. Induction was effected with thiopentone sodium; up to 500 mg was given intravenously. Anaesthesia was maintained with nitrous oxide/oxygen (5 litres/minute and 1.5 litres/minute respectively) in a semi-closed circuit. It has been shown that this anaesthetic com-

bination has little effect on the response to nerve stimulation (Brown, 1955a) or on the tendon-jerks (Brown, 1955b). The reflexes tested were the biceps, triceps, supinator, knee, and ankle jerks. In some patients only the ankle-jerk and the knee-jerk could be used because the arms were being used for other purposes.

The ulnar nerve was used for electrical testing. A low frequency stimulator of conventional design was used. It gave one-millisecond pulses which could be varied in force from 0 to 120 volts. In this study, attention was focused principally on the minimal level of stimulation necessary to produce a muscular response which could just be seen or felt. Single shocks were used at a rate of one per second.

In general the procedure was as follows:

(1) Pethidine hydrochloride was injected into the premedicated patient.

(2) The active electrode from the stimulator was fixed in relation to the ulnar nerve at the elbow. The minimal voltage-setting necessary to produce a twitch was determined. The tendon-jerks were tested.

(3) Anaesthesia was induced. The tendon-jerks were tested. The voltage setting was adjusted, if necessary, to to reproduce a minimal twitch.

(4) A dose of a specific relaxant was given. Pause for five minutes. The tendon-jerks were retested. The voltage-setting was readjusted if necessary.

(5) Another dose of the specific relaxant was given and after a pause for five minutes the tendon-jerks were retested. The voltage-setting was readjusted if necessary.

Step 5 was repeated as often as desired, or as often as circumstances allowed. Some patients were given very large doses of d-tubocurarine or gallamine because the drugs were considered innocuous, provided effective artificial respiration was maintained, and because an efficient antidote existed. No such liberty was taken with decamethonium iodide. All patients were intubated with a cuffed endotracheal tube at a convenient time. If apnoea supervened, artificial respiration was maintained by intermittent manual pressure on the reservoir bag. Investigation frequently proceeded during the operation. In such cases, after the patient had been transferred to theatre, a soda-lime canister was inserted in the circuit, apnoea was induced (if not present), and artificial ventilation was continued with a mechanical pump.

RESULTS

The general results obtained with the three specific relaxants have been compressed, so far as possible, into tables I, II and III. In these tables are recorded the effect of the relaxant on the tendon-jerks, the effect on the response to stimulation of the ulnar nerve, and the dose of relaxant found satisfactory for upper abdominal surgery. The effect on the tendon-jerks is recorded as "unaltered", "enhanced", "failing", or "absent". By "failing tendon-jerks" it is implied that the jerks are still present, or nearly all present, but they are diminished in force as compared with the jerks elicited before giving the relaxant. "Enhanced" tendon-jerks describes the opposite situation—the tendon-jerks, or most of them are exaggerated. The other

terms are self-explanatory. The effect on the response to stimulation of the ulnar nerve is described in relation to the threshold voltage-setting found to give a minimal twitch when the patient was conscious. After the exhibition of specific relaxants, then, the threshold may be said to be "unaltered", "falling", or "rising". A rising threshold implies that a greater stimulus is needed to reproduce a minimal twitch. A falling threshold implies that a lesser stimulus is now enough to reproduce a minimal twitch.

The dose of relaxant entered in the tables as found satisfactory for surgery is not necessarily the lowest dose which would provide satisfactory conditions. It is the first dose tested and found to provide these conditions. Where a grossly excessive dose of specific relaxant has been given for other purposes, it would obviously be unhelpful to tabulate it as "found satisfactory for surgery". In these circumstances, then, the column is left blank.

With the stimulator, three phases of response were distinguished when d-tubocurarine has been given. With a phase 1 response, a series of stimuli at the rate of one per second led to an equivalent series of twitches. (In the tables, a phase 1 response is implied unless otherwise stated.) With a phase 2 response a series

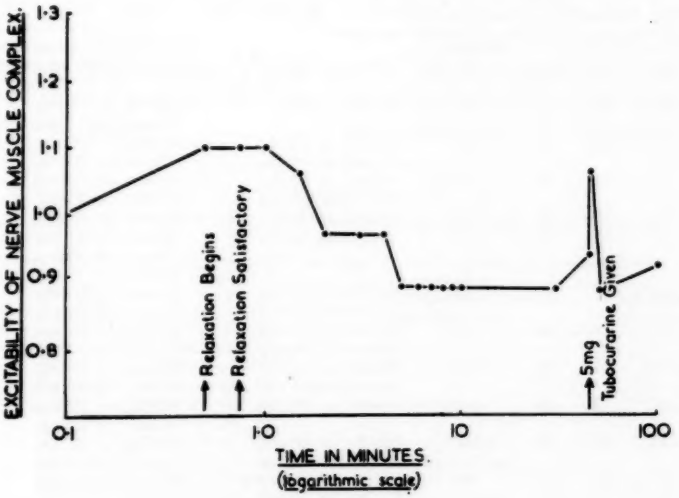

FIG. 1

The time-course of the change in excitability following administration of d-tubocurarine.

Male, age 52; weight 123 lb. (55.35 kg). Initial dose: 20 mg of d-tubocurarine. The ulnar nerve was stimulated, and the voltage necessary just to produce a standard minimal response was taken as "threshold".

Excitability is calculated as the ratio of the threshold-voltage before giving a relaxant drug to the threshold-voltage at the time considered.

It is assumed, for purposes of illustration on a logarithmic time-scale, that no change in excitability occurs during the first six seconds after injection of the initial dose of the relaxant.

TABLE I

The effect of d-tubocurarine on tendon-jerks, response to stimulation of the ulnar nerve, and state of musculature.

(A) NORMAL DOSAGE

Case	Age	Sex	Weight in pounds	Tendon-jerks	Threshold to stimulation of ulnar nerve	Satisfactory for surgery
1	65	F	100	Failing at 15 mg	—	15 mg
2	51	F	—	Enhanced at 20 mg	—	20 mg
3	37	M	115	Enhanced at 20 mg	—	20 mg
4	32	M	117	Failing at 25 mg	—	25 mg
5	60	M	153	Failing at 25 mg	—	25 mg
6	51	M	127	Failing at 15 mg, 20 mg	Unaltered	20 mg
7	57	M	119	Unaltered at 20 mg	Falling at 20 mg	20 mg
8	66	M	103	Failing at 15 mg	Rising at 15 mg	15 mg
9	50	M	140	Unaltered at 20 mg Failing at 25 mg	—	25 mg
10	23	M	134	Unaltered at 30 mg	—	30 mg
11	44	M	137	Unaltered at 20 mg	—	20 mg
12	67	M	158	Failing at 15 mg, 20 mg	Rising at 15 mg, 20 mg	20 mg
13	40	M	125	Unaltered at 20 mg	Rising at 20 mg	20 mg
14	36	M	136	Failing at 20 mg	—	20 mg
15	30	M	118	Failing at 20 mg	Unaltered at 20 mg	20 mg
16	61	M	—	Unaltered at 1.5 mg Failing at 20, 25 mg	Rising at 15 mg	25 mg
17	36	F	91	Absent at 20 mg	Rising at 20 mg	20 mg
18	49	M	146	Failing at 20 mg	Rising at 20 mg	25 mg
19	57	F	108	Absent at 15 mg	Rising at 15 mg	15 mg
20	46	F	119	Absent at 15 mg	Rising at 15 mg	15 mg

(B) SUPRA-NORMAL DOSAGE

Case	Age	Sex	Weight in pounds	Tendon-jerks	Threshold to stimulation of ulnar nerve
21	43	F	122	None elicited	Rising at 15 mg Phase 2 at 25 mg
22	30	M	130	Failing at 20 mg Absent at 40 mg	Rising at 20 mg Phase 3 at 60 mg
23	41	M	133	Failing at 10 mg Absent at 20 mg	Rising at 10 mg Phase 3 at 45 mg
24	56	M	166	Absent at 30 mg	Rising at 30 mg
25	35	M	122	Absent at 30 mg	Rising at 30 mg Phase 2 at 50 mg Phase 3 at 55 mg
26	41	M	166	Failing at 25 mg Absent at 35 mg	Rising at 25 mg Phase 2 at 35 mg
27	28	M	119	Failing at 25 mg Absent at 30 mg	Rising at 20 mg Phase 2 at 30 mg
28	26	M	158	Failing at 25 mg Absent at 40 mg	Rising at 25 mg Phase 3 at 40 mg
29	32	M	112	Absent at 30 mg	Rising at 30 mg Phase 2 at 45 mg
30	31	M	160	Failing at 20 mg Absent at 40 mg	Rising at 20 mg Phase 3 at 45 mg
31	28	M	140	Enhanced at 25 mg Failing at 30 mg	Rising at 25 mg
32	34	M	103	Failing at 20 mg Absent at 30 mg	Rising at 20 mg
33	33	M	130	Enhanced at 20 mg Failing at 30 mg	Rising at 20 mg
34	44	M	126	Absent at 30 mg	Phase 2 at 30 mg Phase 3 at 40 mg
35	31	M	150	Failing at 20 mg	Rising at 20 mg
36	24	M	130	Failing at 20 mg	Rising at 20 mg

A phase 1 response implies that a series of stimuli applied to the nerve at one-second intervals provoked an equivalent series of twitches.

A phase 2 response implies that a series of stimuli applied to the nerve provoked only an initial twitch, or, at most, a short series of twitches of diminishing intensity (Wedensky, 1886).

A phase 3 response implies that a series of stimuli applied to the nerve provoked no twitches whatsoever.

of stimuli at the rate of one per second led to only one response, or at most a short series of responses decaying rapidly. With a phase 3 response, a series of stimuli at the rate of one per second led to no twitch at all in the muscles supplied by the ulnar nerve.

Table I is concerned with the effect of d-tubocurarine. This was the largest group, and it was thought useful to divide the patients into those who were [I(B)] or were not [I(A)] given unnecessarily large doses of the relaxant.

The results in table I(A), concerned with normal doses of d-tubocurarine show that:

(1) It is unnecessary to abolish tendon-jerks completely in order to obtain relaxation satisfactory for upper abdominal surgery.

(2) Commencing failure of the tendon-jerks usually indicates a level of curarization satisfactory for surgery.

(3) A slight rise in the threshold to nerve stimulation is usually an indication of a level of curarization satisfactory for surgery.

The time-course of changes in the threshold to stimulation of the ulnar nerve after a specific relaxant drug has been given is illustrated by a typical example in figure 1. (A logarithmic time-scale is used, so as to show the short-term effects as well as the slower ones.) It will be seen that abdominal relaxation satisfactory for surgery (as judged by the surgeon) precedes the onset of neuromuscular block in the arm muscles, and, in fact, can co-exist with a transitory phase of enhanced excitability in the response to stimulation of the ulnar nerve. Such a phase of enhanced excitability has been found to occur in the majority of subjects examined with this in mind; it precedes the rise in threshold which is presumably associated with the onset of neuromuscular block.

TABLE II

The effect of gallamine on tendon-jerks, response to stimulation of the ulnar nerve, and state of musculature.

Case	Age	Sex	Weight in pounds	Tendon-jerks	Threshold to stimulation of ulnar nerve	Satisfactory for surgery
1	55	F	96	Unaltered at 70 mg	——	70 mg
2	50	M	106	Unaltered at 80 mg	Rising at 60 mg	80 mg
3	32	M	132	Failing at 80, 120 mg	——	120 mg
4	40	M	120	Enhanced at 120 mg Absent at 240 mg	Rising at 120 mg Phase 3 at 360 mg	——
5	52	F	108	Unaltered at 120 mg Absent at 160 mg	Rising at 80 mg Phase 2 at 240 mg	——
6	48	M	113	Failing at 80 mg	——	——
7	40	F	125	Absent at 120 mg	Rising at 120 mg Phase 2 at 160 mg	——
8	44	M	122	Unaltered at 120 mg	Rising at 120 mg	120 mg
9	23	F	109	Failing at 80 mg	Rising at 80 mg	80 mg
10	64	M	133	Unaltered at 80 mg	Rising at 80 mg	80 mg
11	56	F	173	Enhanced at 100 mg	Rising at 100 mg	100 mg

A phase 1 response implies that a series of stimuli applied to the nerve at one-second intervals provoked an equivalent series of twitches.

A phase 2 response implies that a series of stimuli applied to the nerve provoked only an initial twitch, or, at most, a short series of twitches of diminishing intensity (Wedensky, 1886).

A phase 3 response implies that a series of stimuli applied to the nerve provoked no twitches whatsoever.

TABLE III

The effect of decamethonium on tendon-jerks, response to stimulation of the ulnar nerve, and state of musculature.

Case	Age	Sex	Weight in pounds	Tendon-jerks	Threshold to stimulation of ulnar nerve	Satisfactory for surgery
1	66	M	91	Absent at 3 mg	——	Not satisfactory at 3 mg
2	39	M	144	Failing at 4 mg Absent at 6 mg	Rising at 4 mg	Not quite satisfactory at 6 mg
3	48	M	131	Failing at 3 mg	Rising at 3 mg	Not satisfactory at 3 mg (perhaps due to delay)
4	39	F	—	Absent at 3 mg	——	3 mg (brief period)
5	67	F	—	Absent at 3 mg	——	3 mg
6	34	F	78	Absent at 3 mg	Rising at 3 mg	Not satisfactory at 3 mg Fair at 5 mg
7	36	M	117	Absent at 3 mg	Rising at 3 mg	3 mg (fair)
8	57	M	110	Absent at 3 mg	Rising at 3 mg	3 mg
9	57	M	131	Absent at 5 mg	Rising at 5 mg	5 mg
10	41	M	103	Absent at 5 mg	Rising at 5 mg	5 mg

This phenomenon has been further examined and will be discussed in a later paper.

Table I(B), concerned with supra-normal doses of d-tubocurarine, shows that:

(1) Failing tendon-jerks are usually associated with a rise in threshold of stimulation.

(2) A phase 2 response is obtained with a dose of 25–50 mg of d-tubocurarine. The range expressed is unnecessarily large because of large steps in the dosage scale.

(3) Complete block is obtained in a range of 40–60 mg of d-tubocurarine. The range is unnecessarily large because of large steps in the dosage scale.

Table II is concerned with the effect of gallamine triethiodide. It appears that this relaxant produces a series of effects similar at each stage to those produced by d-tubocurarine chloride and shown in Tables I(A) and I(B).

Table III is concerned with decamethonium iodide and the following points emerge:

(1) It was more difficult to obtain surgical satisfaction.

(2) Even when small doses were given, tendon jerks were abolished. This was not necessarily associated with surgical satisfaction.

(3) A rising threshold to nerve stimulation was not necessarily associated with surgical satisfaction.

It may also be noted that endotracheal intubation was found to be relatively difficult with this relaxant.

The effects of high doses of relaxants may be illustrated by case No. 28 in Table I(B). This was a male subject, aged 26, weighing 158 lb (71.1 kg). He was anaesthetized for a partial gastrectomy. Anaesthesia was induced in the standard fashion; 25 mg of d-tubocurarine chloride were then given. This produced a moderate increase in the threshold to stimulation (maximal at ten minutes) and a phase 1 response. It was still possible at this time to elicit knee- and ankle-jerks. Five minutes later, another 15 mg of the relaxant were given. This produced almost immediate abolition of spontaneous respiration and tendon-jerks. The phase of response changed abruptly to type 3. Thirteen minutes later, however, a phase 2 response was found and a further 10 mg

of the relaxant were given. (A total of 50 mg of d-tubocurarine chloride were given in thirty minutes.) The phase 2 type of response returned after another thirty minutes. The operation was now finished, and atropine was given followed by 2.5 mg of neostigmine. Five minutes after the neostigmine had been given, the patient was still apnoeic and there was a phase 2 response. Ten minutes after the injection of neostigmine, a phase 1 response was found, and knee and ankle clonus was elicited. Two minutes later, the patient coughed and started to breathe spontaneously; he opened his eyes; he raised his head.

Similar effects were noted with gallamine triethiodide. With this agent, however, it was very difficult to elicit a phase 3 response. This difficulty may possibly be related to the relatively short action of the drug. A phase 3 response was obtained only once after giving the enormous dose of 360 mg. In another patient, a dose of 240 mg given over a period of twenty minutes, in an attempt to obtain a phase 3 response, produced only a phase 2 response. It was not thought justifiable to pursue this will-o'-the-wisp—purely of academic interest—any further.

DISCUSSION

Relation between tendon-jerks, threshold changes, and surgical satisfaction.

So far as decamethonium is concerned, no clear relation has been made out between effects on tendon-jerks and threshold to stimulation, and surgical satisfaction. It is clear that decamethonium abolishes tendon-jerks at a dosage level less than that required for surgical satisfaction. This is presumably associated with the mode of action of decamethonium. The tendon-jerks can therefore not be used clinically as a gauge of the effectiveness of decamethonium. Equally, no relation has been made out between a rising threshold to stimulation and surgical satisfaction when decamethonium is used.

When d-tubocurarine or gallamine was used, the tendon-jerks were some guide to the effectiveness of the relaxant. It was possible, in some patients, to obtain surgical satisfaction while still preserving active reflexes. Under these conditions, however, there is no clinical indication of adequate dosage other than a trial of surgery. Failing tendon-jerks were in nearly every instance a sign of conditions suitable for upper abdominal surgery. Another indication sometimes found was the development of ankle clonus in response to dorsiflexion of the ankle. In these patients also conditions were suitable for surgery.

A rising threshold to stimulation of the ulnar nerve was also usually associated with conditions suitable for surgery. Complete peripheral block is not achieved unless very large doses of relaxant are used. Abolition of the tendon-jerks occurred while there was a phase 1 response to stimulation of the ulnar nerve. The reason for this is not clear. It will be developed in later work.

There may be some advantage in not completely abolishing tendon-jerks during " curarization ". It is conceivable that excessive " curarization " may lead, without any possibility of protest on the part of the patient, to inadequate anaesthesia. Protest by the patient is usually shown by small reflex movements of the muscles of

the face, the hand, or the foot. It is suggested that if a state of "curarization" is chosen in which the tendon-jerks are not completely abolished, one can rely with more confidence on the patient's ability to respond reflexly to noxious stimuli. It may be that such a state is the safest one to adopt for routine use.

It may be argued that the response to stimulation of the ulnar nerve does not provide a satisfactory index to the state of neuromuscular block in the abdominal muscles. This point has been separately investigated and it has been found (as will be reported later) that the changes in the response of the rectus abdominus muscles to stimulation of the tenth intercostal nerve during successive stages of "curarization" are closely parallel to the changes in the response to ulnar nerve stimulation. Adequate relaxation for abdominal surgery is not incompatible with sufficient integrity of the neuromuscular junctions to permit brisk, palpable, twitches of the rectus abdominus muscle on stimulation of the tenth intercostal nerve.

High dosage effects.

A number of patients, in this investigation, were given very large doses of d-tubocurarine or gallamine. Several interesting features were disclosed. The peripheral block seems in some instances to require more than five minutes to attain its maximum effect. When a large dose has been given, a phase 2 or 3 response may be very persistent. In one patient it lasted for ninety minutes after the last moiety of the dose had been given. A phase 2 response was in three patients found to persist despite the return of spontaneous respiration. No real difficulty was found in restoring adequate respiration at the end of the operation. In many patients there was a marked association between the return of phase 1 response or the return of spontaneous respiration and the regaining of consciousness by the patient. It will be recalled that in a case of very prolonged apnoea following the administration of suxamethonium reported by Cowan (1954) there was a similar association between return of spontaneous respiration and return of consciousness. I do not wish to develop this topic here, but it will be developed in further work.

Stages of "curarization".

Just as the stages of anaesthesia were described in relation to diethyl ether, and the signs of these stages are not necessarily applicable when other agents are used, so the stages of curarization previously were related to various extracts of curare, and are not necessarily applicable to the agents now in common use.

Bremer carried out experiments both on intact and decerebrated mammals. His results are therefore not necessarily completely applicable to observations involving anaesthetized humans. At least six patients in table I(A), however, show that after exhibition of a dose of d-tubocurarine adequate for surgery, their tendon-jerks were either substantially unaltered, or were even enhanced. Two patients in table II show similar signs. It is thought that these patients might reasonably be said to show the "stage of Bremer".

It is more difficult to place the more numerous patients whose tendon-jerks are still present, albeit failing. The reflexes cannot be said to be lively, so the patients

TABLE IV

Relation between the five stages of "curarization".

Stage	Tendon-jerks	Response to stimulation of ulnar nerve	Remarks
1	Lively	Phase 1*	Stage of Bremer
2	Failing	Phase 1 (threshold rising)	——
3	Absent	Phase 1 (threshold still rising)	Stage of Vulpian
4	Absent	Phase 2†	——
5	Absent	Phase 3‡	Stage of Bernard

* A phase 1 response implies that a series of stimuli applied to the nerve at one-second intervals provoked an equivalent series of twitches.

†A phase 2 response implies that a series of stimuli applied to the nerve provoked only an initial twitch, or at most a short series of twitches of diminishing intensity (Wedensky, 1886).

‡A phase 3 response implies that a series of stimuli applied to the nerve provoked no twitches whatsoever.

are not in a "stage of Bremer". However, as reflexes are present, the patients are not in a "stage of Vulpian"; they are in limbo.

We can also find in the tables some patients who are clear examples of the "stages of Vulpian" (reflexes absent) but showing definite phase 1 response to stimulation. We can find definite examples of the "stage of Claude Bernard". Unfortunately there is a larger group of patients who do not properly fit into either category. As the phase 2 response was not described until the time of Wedensky (1886), we must suppose that Vulpian did not encounter it. Patients showing this type of response, therefore, are not examples of the "stage of Vulpian"; nor are they examples of the "stage of Claude Bernard"; they also are in limbo.

From this welter of groups, it is possible to distinguish five stages of "curarization" in anaesthetized patients given d-tubocurarine or gallamine. As the effect of the relaxant drug develops, either with dose-level, or with time after a single dose, the stages of "curarization" may be distinguished as follows:

(1) In the *first stage*, the tendon-jerks are not impaired—some may even be more lively than they were before the relaxant was given. The threshold of response to electrical stimulation is not increased; it may even be slightly lowered (see fig. 1). This stage seems to correspond with that described by Bremer and Titeca. In this stage the muscles were flaccid, but voluntary movement was not abolished, reflexes were lively, and respiration was regular. The effects of the relaxant on voluntary and respiratory muscles are, of course, modified by anaesthesia. Though this stage might provide conditions adequate for surgical purposes, there are few clinical signs of its presence. It may sometimes be distinguished by the appearance of ankle clonus on dorsiflexion of the ankle.

(2) In the *second stage*, the tendon-jerks may be said to be "failing". Some tendon-jerks may be abolished completely. Others are still present, but are less active than they were before the relaxant was given. The threshold of response to electrical stimulation of the ulnar nerve is beginning to rise. Each

stimulus of a series at one-second intervals provokes a separate twitch (Phase 1).

(3) In the *third stage*, the tendon-jerks are abolished. The threshold of response to electrical stimuli is raised, but each of a series of stimuli still provokes a twitch (Phase 1). This stage seems to correspond to the state described by Vulpian.

(4) In the *fourth stage*, the tendon-jerks are absent. The threshold of response to electrical stimuli is further raised, but now a series of stimuli at one-second intervals provokes a twitch only in response to the initial stimulus, or at most, provokes only a short series of twitches of rapidly decaying intensity (Phase 2, or Wedensky inhibition).

(5) In the *fifth stage*, tendon-jerks and the response to nerve stimulation are both absent. This corresponds to the stage of full curarization described by Claude Bernard.

It is suggested that, for routine anaesthetic purposes, it might be reasonable to aim at the second stage—at the point at which the tendon-jerks are starting to fail.

The anaesthetist could then feel: (1) that "curarization" was likely to be adequate; (2) that "curarization" was not excessive; (3) that if anaesthesia became inadequate, the patient would be able to indicate protest by reflex movement.

SUMMARY

Stages of curarization are described on the basis of fifty-seven patients subjected to anaesthesia. d-Tubocurarine chloride was used for thirty-six patients. Gallamine triethiodide was used for eleven patients. Decamethonium iodide was used for ten patients. The basis of assessment was: the effect of the relaxant on the tendon-jerks; the effect of the relaxant on the response to stimulation of the ulnar nerve; and the state of muscular relaxation in relation to upper abdominal surgery.

The effects of normal and large doses of d-tubocurarine and of gallamine are reported. The effects of normal doses of decamethonium are also reported. It is concluded that there are no useful indications of effective dose-level for decamethonium. Five stages of "curarization" are distinguished for the other relaxants used. Indications of adequate dosage with these agents include failing tendon-jerks, enhancement of ankle-jerks, and a rise in the threshold of response to stimulation of the ulnar nerve.

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REFERENCES

Bernard, C. (1856). *C. R. Acad. Sci. (Paris)*, **43**, 825.
Bremer, F., and Titeca, J. (1935). *Arch. int. Physiol.*, **42**, 223.
Brown, R. C. (1955a). *Brit. J. Anaesth.*, **27**, 471.
—— (1955b). *Brit. J. Anaesth.*, **27**, 477.
Cowan, K. A. (1954). *Anaesthesia*, **9**, 23.
Vulpian, A. (1870). *Archives de Physiologie*, **3**, 171.
Wedensky, N. E. (1886). *Ueber die Beziehungen zwischen Reizung und Erregung im Tetanus*, St. Petersburg.

Brit. J. Anaesth. (1955), **27**, 535

PHAEOCHROMOCYTOMA IN A CHILD: ANAESTHETIC MANAGEMENT FOR SUCCESSFUL REMOVAL

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INTRODUCTION

FEW phaeochromocytomata have been reported in children. Daeschner, in 1954, only collected thirteen accounts of operation for their removal in the age group 0–14 years (Daeschner *et al.*, 1954). The first in this country was reported in 1951 (Hubble, 1951). There were seven deaths in this small series.

There are many excellent accounts of these tumours in the literature (Hamilton *et al.*, 1953; Sprague *et al.*, 1953; Graham, 1951; Snyder *et al.*, 1947; Israelski *et al.*, 1953; Conley *et al.*, 1954; Cobb *et al.*, 1953) but few have been written primarily from the anaesthetist's viewpoint. Furthermore, there are discrepancies of opinion, and the sources of pharmacological and physiological information are widely scattered.

A phaeochromocytoma is a tumour of chromaffin tissue which secretes large amounts of adrenaline (adrenaline = a mixture of adrenalin and noradrenalin). It is usually encapsulated, benign (96 per cent), unilateral (85 per cent), and situated in or near the suprarenal bodies (90 per cent).

Operation may be hazardous (20 per cent mortality in 106 operations since 1947 (Morris *et al.*, 1954) but provides the only chance of survival).

The tumour causes adrenaline intoxication, the symptoms of which are: severe frontal headaches, anxiety, sweating, shortness of breath, thirst, polyuria, vomiting, constipation, visual disturbances, and loss of weight.

The signs which may be observed include: hypertension, pallor, dilated pupils, postural hypotension with tachycardia, peripheral vasomotor disturbances, and cardiac failure.

Investigations may show: raised metabolic rate, fasting blood sugar and white cell count. Heterotopic foci with a changing pacemaker occur in the electrocardiogram.

Tests which aid diagnosis include: the production of hypertension (or an increase of hypertension) by the intravenous injection of histamine or methacholine or tetraethyl-ammonium bromide. (T.E.A.B. lowers blood pressure in the normal subject by virtue of its ganglion-blocking properties.)

The ability of adrenolytic drugs to lower a raised blood pressure.

The maximum heat loss test of Pickering (Hamilton *et al.*, 1953)—an assay of peripheral vasoconstriction.

The most useful test is the technically difficult assay of urinary adrenaline.

Location of the tumour site can sometimes be made by excretion pyelography or presacral retroperitoneal pneumo-

graphy, which is safer than perirenal insufflation. In certain cases pressure on the site of the tumour causes a rise of blood pressure.

Blood Pressure.

Hypertension is often the presenting feature and its degree at any time is an indication of the severity of adrenaline intoxication. The hypertension may be paroxysmal at first in adults. The pulse may be either fast or slow, possibly depending on the ratio of adrenalin to noradrenalin secreted by the tumour. As adrenalin and noradrenalin act peripherally, autonomic ganglion blocking agents will not lower the blood pressure. The effect of amyl nitrite is disputed. Hypertensive crises may be induced by drugs, emotion, posture, pressure on the tumour, cold, intravenous transfusion and all forms of surgery and anaesthesia.

Adrenalin and Noradrenalin.

Adrenalin causes overall vasodilatation and increased cardiac output. Noradrenalin causes vasoconstriction and does not directly affect cardiac output.

Adrenalin depresses the spinal cord, raises the serum potassium level and stimulates the secretion of A.C.T.H. (Hunter *et al.*, 1955). A patient receiving an intravenous infusion of noradrenalin has a further rise of blood pressure if given atropine. Moreover the infusion of noradrenalin, especially in high concentration, for long periods, in the aged, and in the lower limb, may cause widespread gangrene of the skin (Sprague *et al.*, 1953; Uricchio *et al.*, 1953). I have seen this.

Adrenochrome, which is an *in vitro* oxidation product, passes the blood brain barrier interfering with cerebral metabolism.

The Risks of Operation.

Inaccessibility and surgical hazards account for only a minor proportion of operative failures. Death, when it occurs, generally takes place either on the operating table or during the first forty-eight hours after operation. Induction of anaesthesia, positioning the patient and manipulation of the tumour can be hazardous. Once the vessels from the tumour have been ligated, a precipitant fall of blood pressure is usual. Postoperative "shock" as manifest by hypotension and peripheral circulatory failure is the commonest cause of death. Pulmonary oedema, haemorrhage and cardiac failure add to the mortality rate.

Various theories have been advanced to explain the facts. According to Burn (1951): "An excessive discharge of adrenaline into the blood stream may depress the conduction of impulses through the sympathetic ganglia preventing the normal stream of tonic impulses reaching the blood vessels."

Gurling and Heriot (1954), however, differ. They consider the fall of blood pressure after removal of the tumour accounted for many more deaths. In Graham's (1951) review, twenty-nine operative deaths occurred in which the tumour was not removed. This is not inconsiderable, and, furthermore, vasopressor substitution has been used for some time.

Some American workers took blood at "the moment of death" from the heart of a child and found the serum potassium to be 13 m.equiv./l. However the agonal

serum potassium changes are probably logarithmic, so I think this may be discounted.

Adrenocortical failure has been instanced as a cause of death (Richards and Hatch, 1951). Both presumptive preoperative hypo- (Hubble, 1951), and hyperfunction (Neff *et al.*, 1942) of the adrenal cortex have been recorded, and the position is unsure, but I assumed in this case that temporary hypofunction might be induced either by interference with both suprarenals should the tumour be bilateral, or by suddenly removing the excess stimulus to secrete.

In those cases associated with polyuria, polydipsia, sodium retention, and increased circulatory volume, the injudicious use of cortisone might prove dangerous (Kositchek and Rabwin, 1950; Conley *et al.*, 1954).

Some phaeochromocytoma appear more dangerous than others. Conley states (Conley *et al.*, 1954): "... It is in these patients with severe paroxysmal hypertension associated with interludes of normotension or sustained hypertension that deaths have occurred during anaesthesia induction for operations unconnected with an unrecognized adrenal tumour .... They show alarming hypertension when the tumour is handled ... and their tumours are extremely vascular and have multiple vascular connections...."

The Adrenolytic Drugs

Developed by Fourneau in 1933, these drugs annul the effects of circulating adrenaline probably by receptor competition. They are not sympatheticolytic in clinical doses.

Dibenamine is long-acting and too toxic.

Benzodioxane (Piperoxane), first used by Goldenberg in 1947 (Goldenberg *et al.*, 1947) is still used both diagnostically and therapeutically. It acts within two to three minutes intravenously, lasting fifteen minutes. Unfortunately, the side effects (tachycardia, dyspnoea, flushing, and in patients without phaeochromocytoma, an alarming rise of blood pressure) restrict its usefulness. Dosage is given in the normogram supplied by the makers.

Phentolamine (Regitine or Rogitine) is the drug of choice, the only notable side effect being moderate tachycardia. It can be given intravenously, intramuscularly or orally. Intravenously the dosage is 5 mg for adults and 1 mg for children, but varies considerably. It acts within two to three minutes lasting rather longer than benzodioxane. Orally it lasts about four hours and has been given for twenty-seven (Iseri *et al.*, 1951) and ten (Daeschner, *et al.*, 1954) days respectively before operation. In the latter case, no noradrenalin infusion was required to restore blood pressure after removal of the tumour.

Chlorpromazine is known to have an adrenolytic action, but it would appear that although, like phentolamine, it antagonizes adrenalin more than noradrenalin, it is less effective than phentolomine (Knox and Slessor, 1955).

Anaesthetic Agents.

Cyclopropane, chloroform, trichlorethylene are contra-indicated. Spinal anaesthesia has induced fatal hypotension *per se*. Gallamine, because of its atropine-like action and tendency to produce tachycardia, is undesirable in theory. Ether

(although it has been used with success in the past) stimulates adrenaline secretion *via* a supraspinal reflex, and a case has been reported where the addition of ether broke down the control obtained by pre-operative phentolamine and continuous infusion of benzodioxane during operation (Bixby *et al.*, 1952).

Because of its ability to "liberate" histamine, curare may produce hypertension in patients with phaeochrome tumours (Knox and Troncelliti, 1955).

CASE HISTORY

On October 22, 1954, David H., 10 years old, was admitted to hospital unconscious. His blood pressure was 90/60 mm Hg, pulse rate 180/min, respiratory rate 40/min and his colour "poor". Knee and ankle jerks were absent and the plantar responses were extensor. The cerebrospinal fluid was normal, but the blood count showed 19,000 white cells per cu.mm (80 per cent polymorphonuclears). His parents stated that for the past six months he had suffered from frequent headaches and vomiting made worse by exercise.

After twenty-four hours he recovered consciousness but later went totally blind for a few hours, and visual impairment with variable central scotomata persisted for a further twenty-four hours. On November 2, 1954, he was discharged to attend the out-patients' department, apparently fully recovered.

On November 12, 1954, he was re-admitted to hospital, pale, pouchy under the eyes, with a blood-pressure of 120/90 mm Hg and severe headache and vomiting. He was retained in hospital for investigation. Intravenous pyelography, urinary microscopy and analysis and an electro-encephalogram were all normal. Blood urea was 22 mg per cent. A tentative diagnosis of migraine was made, and for a while, ergotamine tartrate, 0.5 mg b.i.d., produced a marked improvement. However, his blood pressure continued to rise. On December 28, 1954, the level had reached 145/120 mm Hg. On February 4, 1955, and February 10, 1955 (fig. 1), intravenous benzodioxane produced a fall in his blood pressure, and two weeks later two specimens of his urine were examined at University College Hospital by a direct pressor test on a cat and showed a daily excretion of 800 and 1,000μg of noradrenalin. (Normal 20 μg.)

Presacral pneumography failed to reveal the side of the tumour. Early exploratory laparotomy was decided upon.

Pre-operative investigations showed no overt abnormalities in the electrocardiogram, a corrected basal metabolic rate of +33 per cent, a haemoglobin of 84 per cent, and a prominent left ventricle and unfolded aortic arch in the chest X-rays. The blood pressure record for the month prior to operation is shown in figure 3.

Serum sodium	133	m.equiv.
Serum potassium	4.3	m.equiv.
Serum chloride	104	m.equiv.
Serum alkali reserve	27.3	m.equiv.
Twenty-four hour volume of urine was	500	ml.
Twenty-four hour secretion of total neutral 17-ketosteroids (Tompsett)	3.8	mg
Twenty-four hour secretion of corticosteroids (Norymberski)	6.9	mg

The child weighed 68 lb (30.6 kg.) showed no evidence of cardiac decompensation and appeared not unduly anxious. He looked strikingly pale. Cortisone acetate, 50 mg, was injected on each of the two days before operation, and again on the day of operation.

Management of Operation and Anaesthetic.

The night before operation the child received 10 grains (600 mg) of chloral hydrate. On the morning of operation a cut-down intravenous infusion of 4.3 per cent dextrose in 0.18 per cent saline was set up into an ankle vein in the ward, the limb of a Y-connection to a bottle of blood being clamped.

Pantopon, 1/9 grain (6.6 mg), and scopolamine, 1/300 grain (0.25 mg), were given subcutaneously one hour before operation.

Anaesthesia was induced with 400 mg thiopentone in 2.5 per cent solution injected slowly into the drip tubing, and followed by 13 mg of tubocurarine. The child's lungs were inflated with oxygen, the cords sprayed with 1 ml 4 per cent lignocaine and a No. 5 Magill's oral tube passed under direct vision. These manoeuvres were done between pauses to assess reactions. Immediately on induction the pulse rate rose from 90 to 180 per minute and the blood pressure from 200/130 to 230/170 mm Hg. The stimulus of spraying the cords produced dilatation of the pupils and increased pallor lasting a few minutes.

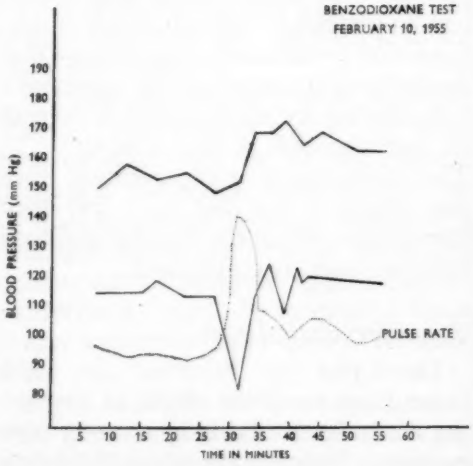

FIG. 1

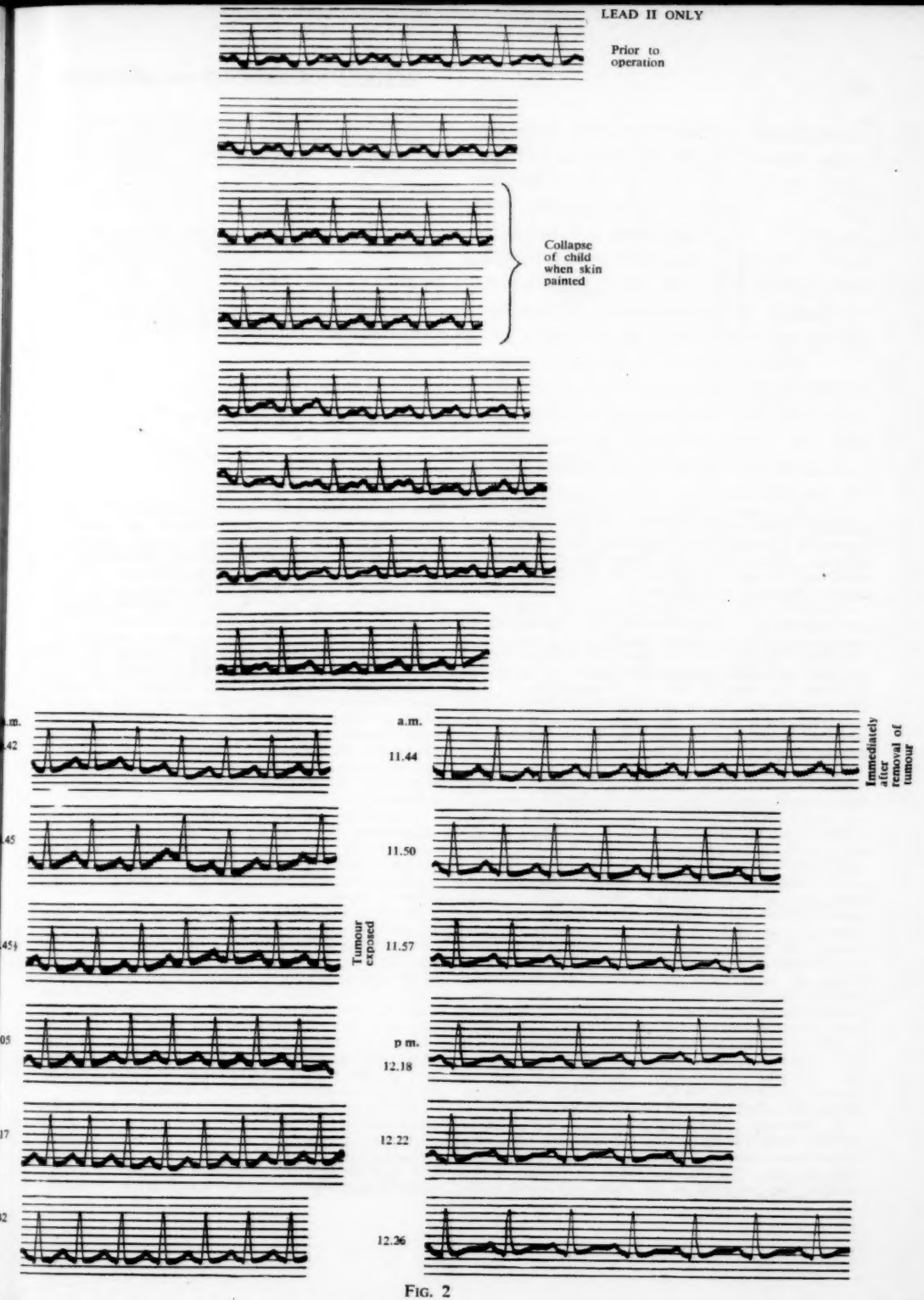
LEAD II ONLY
Prior to operation
Collapse of child when skin painted
a.m.
11.44
Immediately after removal of tumour
11.50
Tumour exposed
11.57
p.m.
12.18
12.22
12.26

FIG. 2

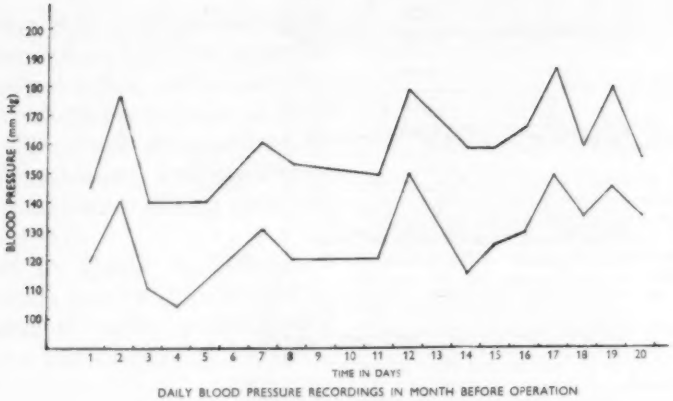

FIG. 3

The child was transferred carefully on to the operating table, where he was placed supine and horizontal, the left arm abducted to facilitate blood pressure readings which were taken every two minutes. Electrocardiograph tracings (Lead II) (fig. 2) were taken at intervals from then on.

Anaesthesia was maintained with nitrous oxide (3 l.) and oxygen (1.5 l.) given through a "to-and-fro" circuit with carbon dioxide absorption and spill over. Further injections of 2.5 per cent thiopentone, 1 per cent pethidine and tubocurarine were given as required. (A total of 500 mg thiopentone, 27 mg tubocurarine and 50 mg pethidine were given over a period of three hours.) Respiration was controlled while the peritoneum was open, and a slow blood drip started after the skin was incised.

Strong spontaneous respiration was present just before the skin was painted with antiseptic, but immediately painting was begun respirations ceased, the pupils became widely dilated, the pulse imperceptible and the blood pressure unrecordable. The continuing electrocardiograph tracing and faint pulsation seen in the xiphisternal notch belied the appearance of death. Pallor was so intense that capillary refill could not be estimated. With cessation of all manipulation and inflation with oxygen the crisis gradually resolved. Because the location of the tumour had not been determined it had been intended to withhold phentolamine until this had been done (Scurr, in a personal communication, reports that handling the tumour failed to produce a rise in blood pressure in one case where 3 mg phentolamine had been given previously) but the plan was altered and a total of 6.5 mg phentolamine was given in divided doses before the tumour was removed. This prevented any alarming hypertensive episodes but had no effect in diminishing the pulse rate which remained at about 200/minute for the whole operation.

A transverse upper abdominal incision was made, initially from the tip of the left eleventh rib to the epigastrium—later extended to the tip of the right eleventh rib. The left suprarenal was normal and a tumour was palpated in the right suprarenal body. This was brought into view by mobilizing the duodenum and hepatic flexure, incising the posterior parietal peritoneum and retracting the liver upwards. Any diagnostic rise in blood pressure on handling the tumour was masked by the phentolamine. A large vein passed from the front of the tumour to the back of the inferior vena cava. As soon as this was clamped the blood pressure fell precipitously to 70/60 mm Hg, and was restored to 150/120 mm Hg by infusion of noradrenalin. Unfortunately, the ligature on the vein failed and a brisk haemorrhage from the back of the vena cava flooded the wound. The blood pressure fell to 90/80 mm Hg and the child's general condition deteriorated alarmingly. Restoration of blood pressure was difficult. One could only guess at the relative requirements of blood and noradrenalin, and, although the haemorrhage could be controlled by pressure, this, in turn, obstructed the nor-adrenalin replacement.

Attempts to find and locate the bleeding point were unsuccessful. Fortunately, the bleeding ceased spontaneously for a while and it was possible to stabilize the blood pressure and shell out the tumour. Afterwards the bleeding stump was ligated and the wound closed in layers.

Spontaneous respiration was allowed to return once the peritoneum was closed. This was rectangular in the first instance, but only for a short while. The child was kept on the operating table for a considerable while (approximately one hour) after the operation ended, as it was felt that a period of recuperation was required before moving him. A few minutes after cessation of the anaesthetic he began to move his limbs, and some fifteen minutes later removed his pharyngeal airway with his hand. Before his return to the ward he had complained of a sore mouth, having momentarily regained consciousness.

The time taken from the first incision to the last stitch was two hours twenty-six minutes. This would have been considerably shorter but for the haemorrhage from the venous stump on the inferior vena cava and the technical difficulties of removing a right-sided tumour by the transabdominal route. However,

it was not thought advisable either to risk turning the child on to his side and make another incision or to repeat operation. A total of 1½ pints (0.86 l.) of blood and 4 ml noradrenalin (1 mg in 4 ml) in 1 pint (0.57 l.) of 4.3 per cent dextrose in 0.18 per cent saline were given whilst the child was in the theatre.

Post-operative Management and Progress.

This was as smooth as the operation was stormy, and throughout the child's general condition was excellent. The blood pressure remained markedly stable at 100–110/80–90 mm Hg although initially it required very large doses of noradrenalin to maintain this level (fig. 4), and the concentration of noradrenalin

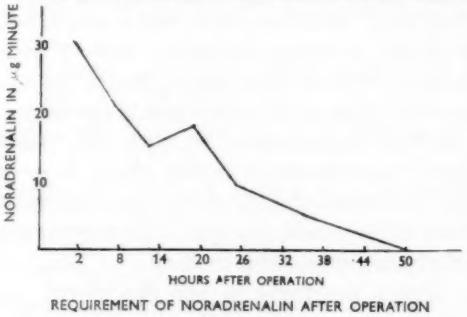

FIG. 4

had to be increased to 16 mg a pint (0.57 l.) for fear of overloading with fluid. Blood pressure recordings were taken every five minutes for forty-eight hours and the drip was then discontinued. The child was kept well sedated, at first with small doses of pethidine given when necessary into the drip, and later with pantopon 1/12 grain (5 mg) subcutaneously. On the first post-operative day, 200 mg cortisone were given intra-muscularly, 150 mg the second day, 50 mg by mouth the third day and a final 25 mg by mouth the day after. There were no postoperative complications save a small area of skin necrosis on his left heel (i.e. near the site of noradrenalin transfusion).

The one disturbing feature was a persistent tachycardia. The pulse rate, which was 200/minute at the end of the operation, fell slowly to 150 over the course of the next eight hours, but only reached the pre-operative level (80–90) again after a further fifteen days. The blood pressure remained remarkably steady at 110/80 mm Hg, there were no further headaches, the child's general condition left nothing to be desired, and he appeared to be losing his pallor.

DISCUSSION

The interesting features of this case are the presence of paroxysmal or sustained hypertension in a child, the severity of the attack on October 22, 1954, the near-fatality due to withholding phentolamine at first, the tachycardia during and after operation, the large dose of noradrenalin required to maintain blood pressure after removal of the tumour, the unexpectedly good postoperative condition, and the unanticipated prolonged rise of urinary cortico- and ketosteroid excretion. It is interesting to note that the tachycardia produced by phentolamine in animals is antagonized by ganglion blocking agents and the alkaloids of *veratrum viride*.

There are five other causes which might contribute to the tachycardia in this case. Unantagonized hypersecretion of the tumour during anaesthetic induction, the prolonged operation, over-estimation of required blood replacement (haemoglobin 103 per cent, packed cell volume 46 per cent six hours after operation) especially in the presence of cortisone therapy, the large doses of noradrenalin given post-operatively,* and the failure of vasomotor reflexes to adjust themselves to the lower blood pressure.

The histological report on the tumour was: " . . . Phaeochromocytoma—the tumour, 3 cm in diameter, was well encapsulated. A small piece of adrenal cortex was included. Section shows the tumour to be composed of loculated areas of round and spindle cells characteristic of the tumour. It is characterized by abundant blood supply. . . ." This would appear to support Conley's statement (see above). It might be preferable in any future similar cases to use oral phentolamine for some days before operation.

ADDENDUM

Since commencing this article David H. has been re-admitted to hospital. There

* Hamilton, *et al.* (1953) showed that noradrenalin in large doses produced a fast, not a slow, pulse rate.

is now a small slough on his left heel and a skin graft is contemplated when the area is clean. He has put on weight, lost his pallor, and maintained his clinical improvement. There has been no further change in his blood pressure. It is now fourteen weeks since his original operation. In view of the fact that he had been given cortisone for a period of six days within the last six months, and a further operation (albeit, a minor one) was contemplated, a Thorn test was done to exclude adrenocortical suppression (Root, 1955). Two consecutive twenty-four-hour specimens of urine were collected, and 50 units of A.C.T.H. gel were injected intramuscularly at the end of the first twenty-four hours. The result of this test and of other ketosteroid estimations are tabulated below (table I). Our present knowledge of ketosteroid excretion is far from complete and unjustifiable speculation is to be condemned. There are reasons for believing the Norymberski method of estimating 17-ketogenic steroids is our best present indication of cortical activity.

The normal values for children, and the effect of operation are being investigated in a control series. We suggest that these values obtained from this one child, indicate, firstly, that three months after his course of cortisone his adrenal cortex was able to respond adequately to stimulation, and, secondly, that the presence of a phaeochrome tumour did not produce any gross cortical over-activity. It is possible that after operation there was a small, but definite, increase of cortical activity prolonged beyond that which might be expected from an uncomplicated operation. Neither the cortisone therapy (all would have been excreted within three days of the cessation of the course) nor the small area of skin necrosis which developed are likely to explain this finding.

From the facts so far elucidated, no strong case can be made either justifying the use of a cortisone "umbrella" or condemning it as an unnecessary precaution.

SUMMARY

The anaesthetic management of a successful operation for removal of a phaeochromocytoma from a child is described.

TABLE I

24-hour 17-Ketosteroid Excretion

	Volume of urine	Neutral ketosteroids	Ketogenic ketosteroids	Na/K ratio
	ml	mg	mg	
Pre-operative 6th day	500	3.8	6.9	—
Postoperative 16th day	510	4.7	11.6	0.75
Postoperative 21st day	620	5.4	8.0	1.1
Postoperative 13th week	520	2.5	5.0	1.73
Thorn Test				
Before A.C.T.H.	720	6.5	11.9	1.23
After A.C.T.H.	350	10.8	35.8	0.81

Na/K ratio is a measure of cortical activity.
The normal adult value is 1.5.
The normal value for children is 2.0.
Lower values indicate greater cortical activity.

The risks of such a procedure, the use of adrenolytic drugs and the effect on adrenocortical secretion are discussed.

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REFERENCES

Bixby, E. W., and Troncelliti, M. V. (1952). *J. Amer. med. Ass.*, **148**, 1443.
Burn (1951). As quoted by Hubble (1951).
Cobb, C. C., Hall, J., and Hall, R. A. (1953). *Lancet*, **1**, 973.
—— —— —— (1953). *Lancet*, **1**, 988.
Conley, J. E., Daniels, E., Belknap, E. L., and End, E. (1954). *Surg. Gynec. Obstet.*, **98**, 177.
Daeschner, C. W., Moyer, J. H., and Able, L. W. (1954). *J. Pediat.*, **45**, 141.
Fourneau, E., and Bovet, D. (1933). *Arch. int. Pharmacodyn.*, **46**, 178.
Graham, J. B. (1951). *Surg. Gynec. Obstet.*, **92**, 105.
Goldenberg, N., Snyder, C. H., and Aranow, N., Jr. (1947). *J. Amer. med. Ass.*, **135**, 971.
Gurling, K. J., and Heriot, A. J. (1954). *Brit. J. Surg.*, **42**, 172.
Hamilton, M., Litchfield, J. W., Peart, W. S., and Sowry, G. S. C. (1953). *Brit. Heart. J.*, **15**, 241.
Hubble, D. (1951). *Arch. Dis. Childh.*, **26**, 340.
Hunter, J. D., Bayliss, R. I. S., and Steinbeck, A. W. (1955). *Lancet*, **1**, 884.
Iseri, L. T., Henderson, H. W., and Derr, J. W. (1951). *Amer. Heart J.*, **42**, 129.
Israelski, M., Kendall, A. C., and Shaw, R. E. (1953). *Arch. Dis. Childh.*, **29**, 18.
Kositchek, R. J., and Rabwin, M. H. (1950). *J. Amer. med. Ass.*, **144**, 826.
Knox, J., and Slessor, A. (1955). *Lancet*, **1**, 790.
Morris, J. C., Robertson, I. F., Stevens, F. R., Grant, R. E., and Stuart, A. E. (1954). *Med. J. Aust.*, **1**, 981.
Neff, F. C., Tice, G. M., Walker, G. A., and Ockerblad, N. (1942). *J. clin. Endocr.*, **2**, 125.
Richards, V., and Hatch, F. N. (1951). *Ann. Surg.*, **134**, 41.
Root, B. (1955). *Curr. Res. Anesth.*, **2**, 78.
Snyder, C. H., and Vick, E. H. (1947). *Amer. J. Dis. Child.*, **73**, 581.
Sprague, R. D., Priestly, J. T., and Kvale, W. F. (1953). *J. Amer. med. Ass.*, **151**, 629.
Uricchio, J. F., Calenda, D. G., and Cutts, F. B. (1953). *J. Amer. med. Ass.*, **152**, 607.

Brit. J. Anaesth. (1955), **27**, 544

INDUCED HYPOTHERMIA FOR RADICAL OPERATION IN CARCINOMA OF CERVIX UTERI

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THE following considerations led to the operation of radical hysterectomy for carcinoma of the cervix uteri being chosen for the first essay into induced hypothermia at the Southern General Hospital, Glasgow. Even in the most expert surgical hands the stress associated with this operation is not inconsiderable, and under conventional anaesthesia the postoperative condition of these patients is often disappointing.

Smith and Fairer (1953) claimed that extensive pelvic operations could be carried out under the modification of Laborit's technique of "hibernation anaesthesia" which they described, and that the patient's reaction to the stress of the operation was less than by the conventional anaesthetic techniques. Also the transfusion of blood could be restricted to replacement of a volume equal to that lost, and that this loss in extensive pelvic clearances amounted to only 300–400 ml blood (Smith and Fairer, 1953). It was also claimed that the hibernation technique could be used for poor surgical risks, even those who ordinarily would be considered unfit for major surgery under general anaesthesia (Smith and Fairer, 1953). This was supported in an Annotation in the *British Journal of Anaesthesia*, published in October 1953, and later received further support from Dundee and Mesham in July 1954.

The work of Dundee, Scott and Mesham (1953) describing the use of the so-called "lytic cocktail" had one important difference from that of Smith and Fairer (1953), viz. the use of lytic cocktail to facilitate the production of hypothermia in animals to which ice was applied. These animal experiments also showed that of the three constituents of the lytic cocktail, viz. chlorpromazine, promethazine and pethidine, the former was the most active agent in the induction of hypothermia.

The technique adopted at the Southern General Hospital conformed to the work of Dundee, Scott and Mesham, the lytic cocktail being administered to render the patient poikilothermic, the body temperature thereafter being reduced by means of surface cooling.

TECHNIQUE

On the evening prior to the day of operation a suitable barbiturate, usually quinalbarbitone 3 grains (180 mg) was administered orally at 7.30 p.m. followed, if necessary, at 10 p.m., by 15 grains (900 mg) each of chloral hydrate and potassium bromide. The chloral and bromide in the same dosage was repeated the following morning. In each case the patient

was scheduled to be in theatre, ready for surgery, at 2 p.m.

Two hours pre-operatively, promethazine 50 mg was administered intramuscularly, followed in one hour by pethidine 100 mg and scopolamine 0.43 mg by the same route. The patient was then transferred to the anaesthetic room which had been cooled as far as possible by shutting off the heating and opening the windows. An intravenous infusion of normal saline was set up into an arm vein to act as a vehicle and diluent for the lytic cocktail. Chlorpromazine, if injected undiluted, may damage the endothelium of the vessel wall and precipitate a thrombophlebitis (Dundee and Mesham, 1954; Churchill-Davidson, 1954). This same reason indicated the injection of the mixture into the drip tubing at some distance from the needle.

Chlorpromazine 50 mg, promethazine 50 mg, and pethidine 100 mg were then drawn into a 10-ml syringe, the total volume of the "mixture" of drugs, usually referred to as the "lytic cocktail", being 6 ml. This was injected as described *via* the drip tubing in four divided doses, viz. 2 ml + 2 ml + 1 ml + 1 ml at $7\frac{1}{2}$-minute intervals, commencing half to one hour pre-operatively. Additional amounts of the mixture were given when necessary.

In view of the depression of the respiratory rate which occurred, oxygen inhalations were started soon after injection of the first 2 ml of the mixture and after the second 2 ml, thiopentone 100–250 mg and suxamethonium chloride 50 mg was administered *via* a vein on the back of the hand or forearm. Orotracheal intubation with a suitable Magill cuffed endotracheal tube was carried out and a wet throat pack placed in position after lubrication of the hard palate and posterior pharyngeal wall with K.Y. jelly. Maintenance thereafter was by a 50 per cent mixture of nitrous oxide and oxygen through Waters' apparatus with soda-lime carbon dioxide absorption.

In the first three cases exposure to the room temperature was all the surface cooling attempted. Subsequently more drastic cooling was applied by the application of ice-bags to the chest wall, abdomen, axillae, and groins, the cooling effect of which were enhanced by a draught of cold air circulating round the patient.

The patient was taken into the operating theatre when the body temperature was falling satisfactorily, but since the rate of cooling was unpredictable, at first the operation tended to be anything up to 40 minutes late in starting. Although it is now found possible to have the patient ready for the surgeon at approximately the proposed time, the great drawback of the technique itself still remains, viz. the inability to control the fall in body temperature accurately to a predetermined level, and similarly the rise in temperature during rewarming.

MANAGEMENT DURING OPERATION

With the patient in position on the operating table, a polythene tube was inserted into the inferior vena cava through the saphenous vein at the groin, to be used for such transfusion as was necessary, and to act as a vehicle for further intravenous medication. Ringer-lactate solution was used until blood transfusion became necessary. The saline infusion into the arm was discontinued and the patient was then ready for operation.

The main reasons for the change from an arm vein to the inferior vena cava were firstly to expedite rapid blood transfusion should the need arise, and secondly the degree of Trendelenberg position (40°–45°, measured by a tiltometer) required by the surgeon would carry the risk of brachial plexus paralysis if an arm was maintained in 90° of abduction throughout the operation.

Muscular relaxation was provided by d-tubocurarine chloride 15–30 mg, sufficient to render the patient apnoeic, being given intravenously just before the operation commenced. In two cases it was found necessary to give a further 100 mg thiopentone at this stage. Throughout operation supplementary doses of d-tubocurarine chloride 5–10 mg were given as required. One case required thiopentone 250 mg during the operation. Manually controlled respiration was carried out, and at the end of operation residual respiratory paralysis was eliminated, if necessary, by intravenous injection of neostigmine 1–3 mg which was preceded, five minutes earlier, by an intravenous injection of atropine sulphate 0.32 mg. This sequence is preferred to including neostigmine and atropine in a single injection, a practice which does not always avoid producing bradycardia.

In order to achieve an approximately accurate replacement of the volume of blood lost, all shed blood was collected on swabs which were carefully weighed.

POSTOPERATIVE CARE

On leaving the operating theatre, the patient was covered by one sheet, and on arrival in the ward the only movement allowed was to transfer her from the theatre trolley to her bed. Oxygen at a flow of four litres per minute was administered through a nasopharyngeal catheter until it was certain that it was no longer required to ensure adequate oxygenation. The limitation of movement and administration of oxygen were precautionary, the former as a safeguard against the hypotension which may be induced by injudicious movement at the end of a prolonged abdominal operation.

Additional blankets were added if shivering occurred, the danger of the burden thrown on the cardiovascular system by shivering having been explained to those concerned. The natural reluctance of nurses to a patient being left more or less uncovered having been overcome, it was possible to indicate that the postoperative nursing care should be as for a similar operation performed under conventional general anaesthesia.

The inferior vena cava infusion was kept running at a slow rate with Ringer-lactate solution for twelve hours, not for the purpose of further fluid replacement, but as a precautionary measure lest massive reactionary bleeding during this time should necessitate immediate blood transfusion.

Apart from an indication that caution should be exercised, no restriction was placed on the prescribing of postoperative sedation by the resident medical staff. Morphine, papaveretum and pethidine were all used, although the preference of the anaesthetist was for pethidine.

Breathing exercises were introduced pre-operatively and continued post-operatively. All ten patients in this series, with the exception of No. 11 (table II), were allowed up to sit on a chair 2–4

days after operation. The exception was a pelvic exenteration carried out on September 16, 1954, after which the patient continued to bleed *per vaginam*, developing a vesicovaginal fistula by November 4, 1954, and a pathological fracture of the upper third of the right femur on December 19, 1954.

Apart from minor changes, the technique has been as described for all ten cases, the most important changes being that in the later cases one intramuscular injection of chlorpromazine 50 mg, promethazine 50 mg and pethidine 50 mg has been substituted in the premedication for the two injections of promethazine, and pethidine and scopolamine: also, in suitable cases rewarming is now hastened by the addition of blankets when the patient is returned to the ward.

INVESTIGATIONS AND RECORDINGS

The cardiovascular, pulmonary and renal systems were investigated pre-operatively. Recording of the blood pressure, pulse rate, respiratory rate and body temperature was begun two hours pre-operatively, and ten-minute recordings made throughout the induction period, during operation, and for one-hour postoperatively. Subsequent readings were made at fifteen-minute intervals, then at thirty-minute intervals, and finally hourly, for twenty-four hours. Rectal temperatures were taken by means of a thermocouple. Blood pressure readings were interrupted in the evening, it being thought more important that the patient should have an undisturbed sleep than that a continuous record should be obtained. The blood pressure was checked if the patient was awake at any time during the night, or if any change in the condition of the patient was suspected. The action of the heart was monitored throughout the operation by means of repeated electrocardiograph tracings, only minor changes, reversible on rewarming, being found.

COMPLICATIONS OF HYPOTHERMIA

In this series neither prolonged hypotension nor prolonged hypothermia were encountered, nor were reactive haemorrhage or postoperative anuria. One patient (table II, No. 7) was oliguric for three days after operation, but thereafter gave no further cause for anxiety. An extensive deep vein thrombosis of the left leg was developed by case No. 9 on the 11th postoperative day, but this event was not thought to be associated with the anaesthetic technique. In case No. 11 a transient mild degree of jaundice appeared the day after operation but cleared up within twenty-four hours. Case No. 16, developed a tachycardia which after persisting for three days settled without treatment. During the period of tachycardia the patient displayed occasional mental confusion.

RESULTS

There have been sixteen patients suffering from carcinoma of the cervix uteri treated by radical operation in the Southern General Hospital between April 1952 and August 1955. The first six of these had spinal analgesia plus general anaesthesia and are shown as a series numbered 1–6 in table I. The remaining ten operated on under the technique described in this paper constitute a second series numbered 7–16, as in tables II and III.

TABLE I

Six cases of carcinoma of the cervix uteri operated on under spinal analgesia and general anaesthesia

Case No.	Age (years)	Operation	Date of operation	Transfusion. Vol. in ml			Postoperative condition	Postoperative sedation, up to 72 hours (mg)
				During op.	Post-op.	Total		
1	51	Radical hysterectomy	16.4.52	1136	—	1136	No information other than that a mild deep thrombophlebitis of left leg occurred on 30.4.52.	Morphine 16 Morphine 16 Morphine 16
2	32	Wertheim hysterectomy	22.4.52 Died 5.12.53	1704	—	1704	No information obtained	Morphine 16 Morphine 16 Morphine 16 Morphine 16 Morphine 16 Pethidine 100 Morphine 16 Pethidine 100 Morphine 16 Pethidine 100
3	31	Radical hysterectomy	20.8.52	568	1136	1704	No information obtained.	Morphine 16 Papaveretum 22
4	30	Radical hysterectomy	13.5.53	1420	852	2272	Fairly satisfactory until wound sepsis developed 18.5.53, and for which wound was opened 26.5.53.	Papaveretum 22 Papaveretum 22 Papaveretum 22 Papaveretum 22
5	44	Pelvic exenteration	6.10.53 Died 8. 10. 53	2272	1704	3976	6.10.53. Placed in oxygen tent on return from theatre, pulse weak, irregular, rapid. Sick reported. 7.10.53. Night report: "Does not look well." Day report: "Condition deteriorated." 8.10.53. Night report: "Condition poor."	Morphine 16 Morphine 16 Morphine 11 Morphine 16
6	50	Radical hysterectomy and lymphadenectomy	15.12.53 Died 16.12.53	2272	1136	3408	Postoperative condition remained poor until death.	Morphine 11

TABLE II

Ten cases of carcinoma of the cervix uteri operated on under general anaesthesia potentiated by hypothermia.

Case No.	Age (years)	Operation	Date of operation	Postoperative condition	Postoperative sedation up to 72 hours (mg)
7	47	Radical (modified Wertheim) Hysterectomy	12.2.54	Satisfactory on return from theatre. 13.2.54. Night report: "Condition satisfactory during night." 15.2.54. General condition excellent, but urinary output not very good.	None
8	45	Radical (modified Wertheim) Hysterectomy	26.2.54	26.2.54. Day report: "Condition satisfactory since return to ward." 27.2.54. Night report: "Condition remains satisfactory."	Papaveretum 22
9	35	Radical (modified Wertheim) Hysterectomy	11.5.54	Condition remained satisfactory until 22.5.54, when an extensive deep vein thrombosis of left leg occurred.	Pethidine 100 Morphine 11 Morphine 11 Pethidine 100
10	47	Radical (modified Wertheim) Hysterectomy	24.8.54	Condition satisfactory on return from theatre. Remained satisfactory throughout convalescence.	Pethidine 100
11	39	Posterior exenteration	16.9.54 Died 22.2.55	16.9.54. Day report: "General condition satisfactory." 17.9.54. Day report: "Slightly jaundiced otherwise satisfactory." 4.11.54. Presence of vesico-vaginal fistula confirmed. 19.12.54. Pathological fracture of upper ⅓ right femur.	Pethidine 50 Papaveretum 11 Pethidine 50 Pethidine 100
12	60	Radical excision of cervical stump and lymphadenectomy	21.12.54	21.12.54. Day report: "Condition satisfactory." 22.12.54. Very peaceful throughout the night. Condition satisfactory.	Pethidine 50
13	62	Radical (modified Wertheim) Hysterectomy	25.3.55	26.3.55. General condition fairly good. Slight productive cough. Sick once.	None
14	54	Anterior exenteration	6.5.55	Uneventful convalescence.	None
15	43	Radical (modified Wertheim) Hysterectomy	17.5.55	Complained only of vague abdominal pain when coughing.	None
16	35	Radical (modified Wertheim) Hysterectomy	25.8.55	Tachycardia with occasional mental confusion until 3rd post-operative day. Subsided without treatment.	Pethidine 100

TABLE III

Anaesthesia, temperature, blood loss and replacement, and blood pressure at end of operation in cases Nos. 7–16

Case No.	"Mixture," ml	Thiopentone, mg	Suxamethonium chloride, mg	Tubocurarine, mg	Neostigmine, mg	Lowest temp., °C	Fall in temp., °C	Duration of operation, minutes	Vol. of blood loss, ml	Vol. of transfusion, ml	B.P. at end of operation, mm Hg
7	6	150	50	30	2.5	35.1	1.7	130	800	1420	115/80
8	6	250	50	55	2	35.6	1.6	105	900	1000	120/80
9	8.5	250	50	30	0	35.6	2.0	120	795	1704	110/70
10	10	200	50	45	3	34.8	2.3	135	426	568	125/90
11	6	450	50	45	1	32.2	3.8	160	2328	2272	160/120
12	6	100	50	40	2	32.8	4.4	140	212	284	120/80
13	7	250	50	30	2	33.8	3.3	145	995	852	170/80
14	6	100	50	30	0	32.8	4.5	180	909	909	120/80
15	7.5	150	50	30	0	31.1	6.0	320	995	1136	80/—
16	7.5	0	50	35	2	31.0	5.2	125	455	455	96/70
Average	7.5	190	50	37	1.4	—	—	156	861	1060	—

Table III shows the figures appertaining to the induction and maintenance of anaesthesia and hypothermia in cases number 7–16. Haemorrhage varied from 212 ml (Case No. 12), to 2328 ml (Case No. 11). The average volume of blood loss, as shown in table III, was 861 ml, while the average volume transfused was 1060 ml. In two cases (Nos. 7 and 9) replacement was in excess of the estimated loss owing to the reluctance of the surgeon to replace a lesser quantity, and also to some extent in other cases by the tendency to finish a bottle of blood, once started, rather than to discontinue the transfusion as soon as the estimated volume had been transfused.

Four of the ten cases required no sedation within seventy-two hours of operation and the average amount for the series over this period was equivalent to 11 mg of morphine (22 mg papaveretum = 100 mg pethidine = 11 mg morphine).

DISCUSSION

It is intended to assess this small series of ten cases (table II, Nos. 7–16), in order to determine if the induction of hypothermia by this technique is of advantage for the treatment of carcinoma of the cervix uteri by radical hysterectomy. Where possible, a comparison will be drawn with the earlier series (table I, Nos. 1–6), operated on under spinal analgesia and general anaesthesia, particularly in respect of the postoperative condition, sedation within seventy-two hours of operation, and blood transfusion. The average ages of the two series are, in table I, 39.5 years (31–51 years) and in table II, 46.7 years (31–62 years). In any comparison there is therefore a slight age advantage to the former group.

Those operated on under hypothermia may be subdivided with reference to the cooling which took place. The first three

cases exhibit only a mild degree of hypothermia, corresponding to the mild surface cooling effect of exposure to a cool environment as described for these cases. The remaining seven, i.e. those subjected to the application of icebags, underwent a moderate degree of hypothermia. Temperatures ranging down to 35°C are regarded as mild hypothermia, between 30°C and 35°C as moderate, and below 30°C as deep.

In so far as this operation is concerned the progression from a fall in body temperature of 1.6°C and 1.7°C to one of 6.3°C has not produced a significant difference in the postoperative condition of the various patients. The main advantage of lower temperatures seems to be in an improvement in operating conditions, due to a reduction in the amount of bleeding which takes place. There is no doubt, however, that the immediate postoperative condition of this series (Nos. 7–16), even those with a minimal fall in temperature, has been much more satisfactory than that of the first series. The latter observation receives support from the nursing staff and from the gynaecologist, both of whom would regard a return to spinal analgesia and general anaesthesia as a retrograde step.

None of the patients operated on under hypothermia died in the postoperative period. Two of the other series did succumb, one twenty-eight hours after operation, the other after twenty hours. In the latter case (No. 6), haemorrhage from a sizeable blood vessel was encountered which could only be controlled by artery forceps being left in position, the patient having to be returned to the ward with the forceps protruding from the wound. Blood transfusion amounted to 3408 ml of blood but the general condition remained poor until death occurred. The other patient (Case No. 5), in the earlier series, who died, became shocked during a prolonged and difficult pelvic exenteration. In spite of transfusion to the extent of 2272 ml of blood in theatre and 1704 ml in the ward, resuscitation was unsatisfactory.

It is noteworthy that in case No. 15, damage to the external iliac vein required it to be ligated. The ligature slipped towards the end of the operation, and the abdomen had to be re-opened. This accident became apparent before the patient had left the operating theatre. Haemorrhage was estimated at 2842 ml and transfusion to the extent of 3410 ml was carried out. The systolic blood pressure had fallen to 35 mm Hg but, with the rectal temperature at 31.2°C, the operation was performed without additional anaesthesia other than the intravenous injection of d-tubocurarine chloride, 7.5 mg. After ligation of the bleeding vessel, the blood pressure was 80/40 mm Hg, and continued to rise as the patient rewarmed.

Further recovery was uneventful, and this patient was sitting in a chair on the second postoperative day, and was allowed to walk on the fourth day.

It has already been noted that the only complications encountered which were likely to be related to the method was mild jaundice and tachycardia. Although it did not cause much anxiety in this particular instance, the former serves as a reminder that the toxicity of chlorpromazine to the liver may be of greater moment than at first believed (Courvoisier *et al.*, 1953;

Anaesthesia, Editoral, 1955; Dundee, 1954). Liver damage, although perhaps not an absolute contra-indication, therefore requires careful consideration prior to embarking on the technique. No major postoperative complications related to the anaesthesia were encountered in the series conducted under hypothermia. Minor respiratory sequelae were remarkably absent.

The volume of blood lost at operation in cases Nos. 1–6 was not recorded. In this group, therefore, blood transfusion must be regarded as fulfilling the dual purpose of blood replacement and the provision of protection from operative shock. Although in the hypothermic series the extent of haemorrhage in each case is known (table III) it is obviously impractical to compare the two series with reference to haemorrhage and transfusion as a means of assessing the amount of protection from the stress of the operation afforded by the two anaesthetic techniques involved.

As noted, however, two cases (table III, Nos. 7 and 9) were overtransfused at the insistence of the surgeon. In the remaining eight cases of this series transfusion of a volume of blood equal to the loss proved adequate to maintain the patients in good general condition. This applied even in case No. 11, in which bleeding amounting to 2328 ml occurred, most of which was lost during a difficult part of the dissection in the last forty-five minutes when the stress of the operation must also have been at its maximum. The inference here is that this type of potentiated anaesthesia does provide protection from the stress of prolonged, severe operation. This is in accordance with the claims of others who have experience of hypothermia. It should perhaps be pointed out that no attempt is being made in this paper to apportion the protection afforded between the action of chlorpromazine (Smith and Fairer, 1954) and hypothermia in considering the response to stress obtained from the technique.

The dosage of anaesthetic agents in the series is also as reported by other workers, viz. a reduction in the amounts used, but as reported by Aronson *et al.* (1954) with respect to Smith and Fairer's method the relaxant drugs were required in approximately the same dosage as in conventional anaesthesia (table III). It may be noted that the volume of blood lost in extensive pelvic operations, as claimed by Smith and Fairer (1953) viz. 300–400 ml under "artificial hibernation", has not, for various reasons, been substantiated in this series, which shows average loss of 861 ml. However, a scrutiny of table III does tend to suggest that with lower temperatures, and provided no inadvertent damage to a main vessel occurs, as in case No. 11, the severity of the bleeding will be reduced.

From tables I and II it can be calculated that the average postoperative analgesia required within seventy-two hours of operation in the first series was equivalent to 55 mg morphine, compared to the equivalent of 11 mg in the second series, four of which required no sedation. With two exceptions in the second series pain was the indication in every instance. On consideration of this it would appear that the severity of postoperative pain experienced by the second series was very considerably less than in the first series. This would contribute to the absence of major respiratory complications, together with

the elimination of heavy postoperative sedation.

CONCLUSIONS

Hypothermia induced by means of the lytic cocktail and surface cooling is of some merit in the radical operation for carcinoma of the cervix uteri.

On the credit side are improved operating conditions, better postoperative condition of the patient, less pain, a reduction in sedation, comparative freedom from postoperative complications and blood transfusion reduced to a minimum. On the debit side is the appearance of one case of jaundice and one other case with a persistent tachycardia and mental confusion.

ACKNOWLEDGMENTS

I am indebted to Dr. A. M. Sutherland and Dr. J. T. Mair, for permission to publish this paper on cases which were under their care. My thanks are also due to Dr. A. K. Boyle for his help and encouragement in the management of this series.

REFERENCES

Annotation (1953). *Brit. J. Anaesth.*, **25**, 345.

Aronson, H. B., Duffield, J. R., Francis, B. G., and Ginsberg, H. (1954). *S. Afr. med. J.*, **28**, 823.

Churchill-Davidson, H. C. (1954). *Postgrad. med. J.*, **30**, 346.

Courvoisier, S., Fournel, J., Ducrot, R., Kolsky, M., and Koetschat, P. (1953). *Arch. int. Pharmacodyn.*, **92**, 305.

Dundee, J. W. (1954). *Brit. J. Anaesth.*, **26**, 357.

—— Scott, W. E. B., and Mesham, P. R. (1953). *Brit. med. J.*, **2**, 1244.

—— Mesham, P. R. (1954). *S. Afr. med. J.*, **28**, 585.

Editorial (1955). *Anaesthesia*, **10**, 3.

Smith, A., and Fairer, J. G. (1954). *Brit. med. J.*, **1**, 212.

—— —— (1953). *Brit. med. J.*, **2**, 1247.

Brit. J. Anaesth. (1955), **27**, 554

AN AID TO INTRAVENOUS ANAESTHESIA

BY

E. F. AUBERT

Princess Elizabeth Hospital, Guernsey

MODERN anaesthetic techniques more and more often require the intravenous administration of anaesthetic agents. Multiple venepunctures during an operation are neither convenient nor desirable; furthermore, if the patient's arm is extended sideways on a splint to provide access to a vein, it may get in the way of the surgeon or his assistant, and the practice is, in any case, not entirely free from danger.

In order to meet these difficulties my partner, Dr. R. B. Sutcliffe, has designed for my use a robust three-way tap, fixed on a metal tube which can be clamped rigidly to the top of the reducing valve of a standard nitrous oxide or oxygen cylinder (fig. 1). To the vents of the three-way tap are attached (*a*) a saline drip, (*b*) about 4 feet of fine polythene tubing (Allen & Hanbury's No. 2, bore 1 mm) with a No. 1 needle at its distal end, and (*c*) a syringe containing the intravenous agent.

At the start of the anaesthetic the needle at the end of the polythene tubing (*b*) is inserted into the patient's vein and secured in position with strapping. The saline drip is then turned on: its sole purpose is to keep the circuit patent. The inducing agent (e.g. thiopentone) is next given from the syringe attached to vent (*c*) by turning

FIG. 1

the tap; it passes so quickly through the polythene tubing on account of its fine bore that it reaches the patient's circulation almost immediately. The saline drip is then re-established. At this stage the patient is transferred to the operating table (care being taken not to dislodge the intravenous needle); the patient's arms are arranged comfortably at the side of the body and are not disturbed again until the end of the operation.

Further anaesthetic agents (e.g. relaxants, pethidine, hypotensive agents, etc.) can then be given as required through vent (*c*). If blood has to be transfused it simply replaces the saline, but wider polythene tubing (size 4 or 5) must then be used; the tubing can be changed at any stage of the proceedings. If the patient is to be sent back to the ward with a drip, it is merely necessary to extract the three-way tap from the circuit.

All connections are of the Luer lock type. The three-way tap, needles, connections, syringes, and polythene tubing are all sterilized by boiling.

The system has been in use for nearly two years and has proved most reliable and satisfactory.

The three-way tap and stand can be obtained from Messrs. Down Bros., Mayer & Phelps, Ltd., 92–94 Borough High Street, London, S.E.1.

The great help given by Mr. Somervell of the above firm has been much appreciated.

Brit. J. Anaesth. (1955), **27**, 556

BRONCHUS TUBE AND BRONCHUS BLOCKER

BY

ROBERT MACINTOSH AND R. A. L. LEATHERDALE

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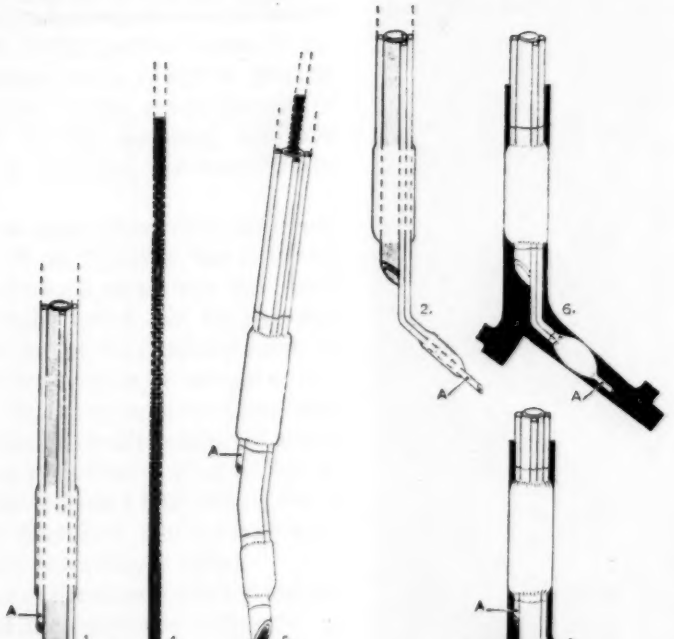
THIS preliminary communication is not concerned with the indications for one-lung anaesthesia, but describes a means of allowing this to be carried out. We believe the method offers the following advantages:

(1) Once in position the endobronchial tube (fig. 1) or the endobronchial blocker (fig. 2) is not dislodged easily since it is tailor made: its shape conforms closely to the course of the trachea and left main bronchus.



FIGURES

(2) The tube or the blocker can be passed "blindly", i.e., without the help of a bronchoscope.

(3) A small tube (A in figs. 1 and 2) is incorporated which can be used either to aspirate secretions from the non-functioning lung or to distend it with oxygen, at the surgeon's request, to facilitate dissection.

Endotracheal tube

If the right lung is to be operated on the shaped tube is passed into the left main bronchus (fig. 3).

Thiopentone and a short-acting relaxant are administered and the larynx and trachea sprayed with a topical analgesic solution. The tube is passed through the cords under direct vision, and the laryngoscope discarded. The tube is advanced when, because of its shape, it will probably enter the left bronchus, and comes to a stop when the angle of the tube is halted at the carina. The distal end of the tube now lies just short of the upper lobe bronchus (fig. 3). The endobronchial cuff is now inflated, and, if desired, the endotracheal cuff. Through the small tube (A in fig. 3) oxygen can be fed to the right lung, or secretions aspirated from it.

If the tip of the tube should enter the right and not the left bronchus, recourse is made to a firm rubber director (fig. 4) whose shape is based on Griffin's (1949) bronchial aspirator. The tube is withdrawn and eased over the director (fig. 5), the tip of which is guided into the left main bronchus. The tube is now pushed down into position, and the director is withdrawn.

Endobronchial blocker (Mülly and Hossli, 1955; Stürtzbecher, 1953)

When the left lung is to be operated on a cuffed endotracheal tube is used in which a blocker is incorporated: the latter is angulated so that it enters and lodges comfortably in the left main bronchus. When the cuff surrounding the blocker is inflated the left lung is isolated (fig. 6). When the anaesthetic bag is compressed only the right lung expands. The blocker, however, is hollow (A in fig. 6) and can be used either to supply oxygen to the left lung or to aspirate fluid from it.

This blocker has been used in two cases of bronchopleural fistula. It was passed and its position checked without difficulty under local analgesia alone.

As the type of blocker described here can be located without the help of a bronchoscope, it should be possible to use smaller sizes for children. A slight variation in design (lengthening of the tubing carrying the bronchus blocker) would make it possible to locate the cuff distal to the opening of the upper lobe bronchus.

The illustrations are diagrammatic: the finished articles are considerably more streamlined than indicated. They are obtainable from Messrs. Medical and Industrial Equipment Ltd., 10/12 New Cavendish Street, London, W.1.

The construction of the endobronchial tube and the blocker would not have been possible without the advice and help so freely given by Mr. R. W. Lunn, C.B.E., of the Leyland and Birmingham Rubber Company, and Mr. R. Salt of this Department.

REFERENCES

Griffin, J. L. (1949). *Brit. med. J.*, **1**, 1000.
Mülly, K., and Hossli, G. (1955). *Der Anaesthesist.*, **4**, 107.
Stürtzbecher, F. (1953). *Der Anaesthesist.*, **2**, 151.

ON CHLOROFORM AND OTHER ANÆSTHETICS

THEIR ACTION AND ADMINISTRATION

BY

JOHN SNOW, M.D.

Licentiate of the Royal College of Physicians

(*Continued from page* 502)

It was often the practice to render the patient insensible in as short a time as half a minute, when chloroform was first introduced, but I believe never without danger; and I had expressed the opinion before any accident happened, that, for reasons such as I have stated above, a patient should on no account be rendered insensible in less than two minutes.*

Case 2. The next recorded case in which the inhalation of chloroform was fatal, occurred at Cincinnati, on the 23rd of February, 1848. The subject of it, Mrs. Martha G. Simmons, was thirty-five years of age, and enjoyed good general health; she was the mother of six children, and her last confinement occurred eight weeks before her death. The patient exhibited no alarm on account of inhaling the chloroform, which was administered by two dentists, who were not members of the medical profession. It was breathed from an inhaler which Dr. Morton of Boston contrived for sulphuric ether. This inhaler consisted of a glass globe four inches and a half in diameter, and contained a sponge about one third filling the globe, and saturated with chloroform.

Two female friends of the patient reported the following as the events which occurred, "The respiratory movements appeared to be free; chest heaving. While inhaling, the face became pale. At the expiration of about one minute, the instruments were applied, and four roots of teeth extracted. The patient groaned and manifested what they regarded as evidences of pain, while the teeth were being extracted, although she did not speak or exhibit any other sign of consciousness. As the last root came out, which was about two minutes from the beginning of the inhalation, the patient's head turned to one side, the arms became slightly rigid, and the body drawn somewhat backwards, with a tendency to slide out of the operating chair. At this instant, Mrs. Pearson states that she placed her finger upon the patient's pulse; observed that it was feeble, and immediately ceased to beat; respiration also ceased about the same time. The face, which was previously pale, now became livid, as did also the finger nails; and the lower jaw dropped, and the tongue projected a little at one corner of the mouth, and the arms were perfectly relaxed. The females regarded her as being then quite dead."†

The dentists gave nearly the same account, saying that the breathing was at first slow, and that the patient inhaled twelve or fifteen times, occupying from a minute to seventy-five seconds. They committed the great error of not placing

* London Medical Gazette, vol. xli, p. 75.

†London Medical Gazette, vol. xlii, p. 80, from Western Lancet, and Phil. Med. Exam. April 1848.

the patient at once in the horizontal position, when the alarming symptoms came on, but kept her sitting in the chair, from five to ten minutes, whilst they sent out for restoratives. They thought the patient was living during this time, but her female friends thought not. The patient was placed on a sofa, and sometime afterwards artificial respiration and galvanism were applied without effect.

An examination of the body was made twenty-six hours after death by Drs. Mussey, Lawson, Baker and Mulford. The following are the chief particulars of the appearances met with. A larger quantity of blood than usual flowed from the sinuses of the dura mater. General aspect, colour, and consistence of the the brain, normal. Lungs considerably but not intensely congested; crepitated freely at all points; no extravasation. Lining membrane of bronchia slightly congested, apparently the result of recent catarrh; deeply stained by the blood. Pleura at all points highly injected; six drachms of bloody serum in the right, and two ounces in the left chest. Pericardium contained six drachms of bloody serum. Heart flaccid, and all its cavities entirely empty; inner surface of both ventricles and auricles deeply stained. Abdomen—one ounce and a half of bloody serum in the right hypochondrium. Stomach and intestines distended with gas. Partially digested aliment, amounting to about three gills in the stomach. Blood fluid as water in every part of the body; not a coagulum was seen in any vessel. Lining membrane of all the bloodvessels deeply stained. The colour in every part of the system was that of dark venous blood.

It was estimated, in the inquiry which took place respecting this case, that one-fourth part by measure of what the patient inhaled might be vapour of chloroform; but this is evidently an over-calculation, for there could not be this quantity unless the interior of the glass globe were maintained at the temperature of 80° Fah. and the air were quite saturated with vapour in passing through it; however, less than half the amount of vapour here assumed would have the effect of causing sudden death, in the way it happened. The period of the inhalation, a minute or seventy-five seconds, during which the patient took twelve or fifteen inspirations, did not admit of the blood in the body being regularly and uniformly charged with the chloroform; and the increase of its effects, owing, no doubt, to the absorption and circulation of the vapour contained in the lungs at the moment when the inhalation was discontinued, was well marked. The patient became pale during the inhalation, but the alarming symptoms suddenly came on during the extraction of the fourth stump, probably within half a minute after the inhalation ceased. The patient seemed, in fact, to die with the slight struggle that took place at this moment. In the case of Hannah Greener, related above, the spasm at the moment of dying was even more marked. This is a symptom I have often seen during the death of animals killed suddenly with vapour of chloroform in a concentrated state, before they were made thoroughly insensible. Although the heart was empty, the stained condition of its cavities showed that they had contained blood at the time of death and afterwards. Owing to its fluid state, it probably escaped from the heart during the moving of the

body; especially during the examination of the head which was made first.

Case 3. The next recorded case of death from chloroform is reported by Dr. John C. Warren, of Boston, U.S., in the *London Medical Gazette*.* His report, apparently extracted from some other report is as follows.

"Name—Patrick Coyle. [Age—not stated.] Date—March 1848. Disease—fistula. Previous use of chloroform—once. Time of inhalation—about one minute. Quantity consumed—about thirty drops. [Query minims.] Posture—upon the side. Lapse of time till death–about one minute. Symptoms—showed signs of pain by putting his hand to the part; in a moment his pulse, which was full and natural, sank: death. Morbid appearances—brain with membranes, natural and healthy. Heart enlarged, pale, and soft; two or three ounces of serum in pericardium; blood-vessels with dark fluid blood. Lungs, studded with tubercles; abscess in each; lower parts congested; pleura extensively adherent; stomach—mucous membrane softened, its veins turgid."

Nothing is said about the apparatus used in this case, but from the summing-up of Dr. Warren's paper, it must have been either a towel or a handkerchief. The quantity of chloroform employed appears to have been much less than in the two previous cases. In speaking of drops the writer, probably means minims, or what is the same, a quantity equal to as many drops of water. Thirty drops of chloroform from a small phial are only equal to between six and seven minims, and if they were dropped on a handkerchief, so that they might be counted, they would evaporate entirely during the process. Supposing the quantity used to have been what is probably meant—half a fluid drachm—it would be quite adequate, according to calculations previously made in these pages, to cause the accident which happened. The period of inhalation was again very short—one minute; and the evidence of paralysis of the heart is distinct:—"In a moment his pulse, which was full and natural, sank: death."

Case 4 was that of Madlle. Stock, aged thirty, and occurred at Boulogne, in May 1848. The operation was that of opening a sinus in the thigh, between two and three inches in length, at the bottom of which a small splinter of wood was found. M. Gorré, the surgeon who attended the patient, says: "I placed over the nostrils of the patient a handkerchief moistened with fifteen to twenty drops of chloroform at most." It is necessary to remark, however, that a judicial examination of the bottle from which it had been taken, proved that from five to eight grammes had been used, a quantity equal to from 77 to 123 grains, and there are three drops of chloroform to a grain. M. Gorré proceeds to say: "Scarcely had she taken several inspirations, when she put her hand on the handkerchief to withdraw it, and cried with a plaintive voice, 'I choke.' Immediately the face became pale; the countenance changed; the breathing embarrassed; and she foamed at the mouth. At the same instant (and certainly less than a minute after the beginning of the inhalation), the handkerchief moistened with chloroform was withdrawn." M. Gorré performed the operation, but he expressed, the opinion afterwards that

* Vol. xliii, p. 682.

death had already taken place when he made the incision. Amongst the means used, with a view to resuscitate the patient, was inflation of the lungs, which was performed with such force as to produce permanent dilatation of the air cells. The lungs, besides being distended from this cause, were found after death to be visibly engorged in their lower lobes. When cut into, a large quantity of black blood escaped. The cavities of the heart were empty, but the internal membrane, especially of the right cavities, was red. The tissue of the heart was pale, and was easily torn. Air was found in the pulmonary veins, and in most of the systemic veins throughout the body. The blood was very dark-coloured and fluid.*

M. Gorré reported the above case to the Academy of Medicine of Paris, and a commission was appointed to inquire and report on it, who came to the following conclusions.

"1. In the medico-legal fact submitted to our notice, we found no indication of the poisonous action of chloroform; and consequently we reply to the minister, that the patient of M. Gorré did not die from the effect of inhalation of that agent.

"2. There have occurred a great number of analogous cases of sudden and unforeseen death, during operations, without any administration of chloroform, in which the most minute examinations have failed in detecting any assignable cause of death.

"3. In the case in question, the most probable cause, under all circumstances, seems to have been the mixture of a considerable quantity of gas with the blood."†

The report on this case gave rise to frequent discussions in the Academy, extending over several months, and the Academy ultimately confirmed the above conclusions, but not without considerable opposition from M. Blandin, M. Jules Guérin, and other members.

M. Malgaigne, the reporter to the commission, and others who strongly supported the first of the above propositions, founded their argument chiefly on the assertion that chloroform always produces intoxication and insensibilty before death; but this is incorrect, as I have explained above; and I took occasion to make the following remarks on this point about the time when the discussion in the Academy of Medicine took place. I said: "I have several times made animals—small birds, mice and rabbits—breathe air saturated with vapour of chloroform at the temperature of the atmosphere, and the consequence has always been that, after attempting for a few seconds to escape from the capacious jar in which they were enclosed, they suddenly exhibited signs of distress, and died without any interval of intoxication or insensibility, in periods varying from less than half a minute to a minute after their first exposure to the vapour."‡

The power of chloroform to cause sudden death without previous insensibility is now, I believe, generally admitted. The French call this kind of fatal action *sideration*.

With regard to the second conclusion of

* Gazette Médicale, 8 Juillet, 1848; and London Medical Gazette, vol. xlii, p. 211.

† Proceedings of Academy on Feb. 6th, 1849. See London Journal of Med., 1849, p. 307.

‡ London Journal of Medicine, 1849, p. 324.

the commission, if it had been really true that the surgeon put only fifteen to twenty *drops* at the most of chloroform on the handkerchief, one would have been inclined to admit it; but with the quantity actually employed, and the strong sensation of choking it occasioned just before death, one must, in connection with other cases, and with what is known of the action of chloroform, attribute the fatal event to this agent, rather than to the surgical operation, which was not of a serious nature.

With regard to the third of the above conclusions, it is not a little remarkable that most even of those speakers who opposed the conclusions of the commission, agreed that death was caused by a sudden development of air in the veins; and differed from them only in this, that they considered the chloroform as the cause of the evolution of air or gas, and that it proved fatal in this way. That the air was not caused by putrefaction, and that it did not enter by the wound in the thigh, may be readily admitted, but there remains the artificial respiration, which was performed with such force as to produce permanent dilatation of the air-cells. It was argued in the Academy that, as the air was in the systemic, as well as in the pulmonary veins, it could not have been introduced by the artificial respiration, since the left ventricle had previously ceased to act; but the action of the left ventricle is not necessary for the passage of the contents of the arteries through the capillaries into the veins, since this commonly goes on after death, the arteries being usually found entirely empty of the blood they must have contained at the moment of death. With regard to the passage of the air out of the heart into the arteries, supposing that the pulmonary veins were ruptured during the inflation of the lungs, there is an observation of Dr. Sibson's which will explain both this circumstance and the fact of the heart itself being found empty of blood. He found that the heart was often emptied of blood by distending the lungs with air after death in preparing the body for his diagrams of the position of the viscera.*

With the conclusions above quoted, some additional ones were adopted from the second part of the report of the commissioners; in these it was admitted that chloroform is capable of causing death, if administered too long, or in too large doses. One of these additional conclusions, however, is as erroneous as the previous ones. It is, "there is a risk of asphyxia when the anæsthetic vapour is not sufficiently diluted with air." When the vapour is not sufficiently diluted with air, the risk is one of sudden death, by paralysis of the heart. Chloroform does not yield enough vapour, at the natural temperature and pressure of the atmosphere, to exclude the air to the extent which would cause asphyxia. When chloroform vapour largely diluted with air is long continued, it may cause, not real asphyxia, but a mode of death resembling it, owing to the medulla oblongata and nerves of respiration becoming over narcotised.

* Lond. Med. Gaz., vol. xliii, p. 694.

(*To be continued*)

LIVERPOOL SOCIETY OF ANAESTHETISTS

PROGRAMME 1955–1956

Friday, October 28, 1955

Dr. Robert Forbes, Secretary of the Medical Defence Union: "The Medico-Legal Aspects of Anaesthesia."

Wednesday, November 30, 1955

Dr. J. Pugh Thomas: "The Use and Abuse of Intubation."

Dr. J. Marchant: "Premedication."

Wednesday, January 25, 1956

Dr. J. Halton: "Off the Record."

Friday, February 24, 1956.

Papers by Registrars.

Friday, March 23, 1956

Dr. G. S. W. Organe: "Some Reflections on the Muscle Relaxants."

Thursday, April 19, 1956

Joint Meeting with the Anaesthetic Section of the Manchester Society of Anaesthetists at Manchester.

Dr. J. E. Riding: "Some Aspects of Post-operative Vomiting."

Dr. T. Dinsdale: "Facts and Fancies."

Friday, May 11, 1956

Annual General Meeting.

SOCIETY OF ANAESTHETISTS OF HONG KONG

THE Second Annual General Meeting of the Society of Anaesthetists of Hong Kong was held on September 15, 1955, at the University of Hong Kong Alumni Association.

The following officials and committee members were elected:

Hon. Secretary and Treasurer: Dr. P. S. Chau

Chairman: Dr. Z. Lett

Committee Members:

Surg. Capt. A. S. Sinclair — Maj. J. K. Sugden
Dr. H. P. L. Ozorio — Dr. Y. O. Chan
Dr. A. J. F. Eberle

SOCIETY OF ANAESTHETISTS OF THE SOUTH-WESTERN REGION

IT is announced that the next meeting of the above society will be held on November 25 and 26, 1955, in Bristol. The meeting in Oxford will be held on June 22 and 23, 1956.

GLASGOW AND WEST OF SCOTLAND SOCIETY OF ANAESTHETISTS

SYLLABUS 1955–1956

Saturday, October 29, 1955.

Joint Meeting with Association of Anaesthetists of Edinburgh in the Royal Faculty of Physicians and Surgeons, Glasgow.

Mr. J. Schorstein (West of Scotland Neurosurgical unit): "Investigations of Consciousness."

Tuesday, November 15, 1955.

Dr. Alistair F. MacLean (Stobhill General Hospital): "Hypnosis."

Thursday, January 19, 1956.

Dr. A. Cameron MacDonald and Dr. H. H. Pinkerton (Western Infirmary); "CO_2."

Thursday, February 23, 1956.

Members' Night.

Friday, March 23, 1956.

Presidential Address: Dr. Albert Christie.

Wednesday, May, 2, 1956.

Annual General Meeting.

The Meetings are held at the Royal Faculty of Physicians and Surgeons, 242 St. Vincent Street, Glasgow, C.2, at 8.15 p.m. Tea is served from 7.45 to 8.15 p.m.

PAKISTAN ASSOCIATION OF ANAESTHETISTS

NOTICE has been sent to us of the formation of the above Association. It has as its objects:

1. To form into a strong union of all the doctor-anaesthetists in Pakistan, so that it would be possible to be recognized by and affiliated to similar medical institutions in the principal countries of the world.
2. To spread instruction and knowledge of anaesthesiology amongst the members by meetings and by circulation of literature.
3. To organize and raise the standard of practice of anaesthesia in Pakistan.
4. To raise the status of anaesthetists in Pakistan.
5. To advise the Government, Universities, Teaching institutions, etc., in whatever manner the association consider fit to further the progress of the science and art of anaesthesia.
6. To help the Universities in Pakistan in the instruction of postgraduates for the diploma in anaesthetics and in holding the examination.
7. Other aims and objects as determined from time to time by the Association.

The Headquarters of the Association will be in Karachi and it will be divided into West and East divisions. Each division will form into direct groups according to geographical areas to enable members to hold meetings and discussion groups. When possible Annual Conferences of all anaesthetists of both the divisions will be held alternately in each division.

At a special meeting held on July 24, 1955, the following officials and Committee members were elected:

President: Surg. Lt.-Cdr. F. N. Taraporvala
Vice-President: Dr. A. M. Attar
Secretary & Treasurer: Surg. Lt.-Cdr. Shaikh Rahman
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FACULTY OF ANAESTHETISTS OF THE ROYAL COLLEGE OF SURGEONS OF ENGLAND

SCIENTIFIC MEETING

IT is announced that a further Scientific Meeting of the Faculty of Anaesthetists will be held at the College on Saturday, May 5, 1956. Further details will be announced later.

BOOK REVIEW

De Narcose (1st edition). By Dr. S. A. Klein, Anaesthetist to the Gemeente Ziekenhuizen at the Hague. Published by De Erven F. Bohn N.V., Haarlem, 1954. Pp. 330; 22 illustrations. Price F.17.50.

The anaesthetic lamps are lighting up one by one in Europe. As one country after another offers its people the incomparable benefits of modern anaesthesia, aspirants to anaesthetic skill demand instructive literature in their own language. For the first time a textbook of anaesthetics in the Dutch language has been written. The reviewer's knowledge of Dutch is small, and he cannot claim to have appreciated and savoured fully either the factual or literary content of the book. Nevertheless, sufficient can be gained by turning the pages, to see that Dr. Klein, a well-known and experienced anaesthetist, writes with enthusiasm and spirit and with more than a little humour. His book covers the main field of clinical anaesthesia. The many references to current English literature show once more how great is the influence of British and American ideas on the development of this specialty in Holland, which is served by a group of well-trained and enthusiastic anaesthetists (to whom visitors to the World Congress owe so much gratitude). A considerable number of anaesthetics, however, are still administered by nurses: it is to these as well as to physicians that Dr. Klein's book is directed.

The general production of the book is of a high order and a compliment to the publishers. We wish the book every success and feel certain it will improve still further the standard of training of Dutch anaesthetists.

W. W. Mushin

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